Tranexamic acid in the routine treatment of postpartum hemorrhage in the United States: a cost-effectiveness analysis

Leanna S. Sudhof, MD; Scott A. Shainker, DO, MS; Brett D. Einerson, MD, MPH

BACKGROUND: The World Maternal Antifibrinolytic trial demonstrated that tranexamic acid administered during postpartum hemorrhage reduces hemorrhage-related mortality and laparotomies. The World Health Organization has thus recommended early use of tranexamic acid in the treatment of postpartum hemorrhage. This recommendation has not been universally adopted in the United States, in part because of concerns about cost-effectiveness.

OBJECTIVE: We aim to demonstrate the cost-effectiveness of routine tranexamic acid administration in the treatment of postpartum hemorrhage in the United States, where the rate of hemorrhage-related mortality is lower than that described in the World Maternal Antifibrinolytic trial.

STUDY DESIGN: We constructed a decision tree comparing 3 strategies in women with a clinical diagnosis of postpartum hemorrhage: no tranexamic acid, tranexamic acid given at any time, and ideal use of tranexamic acid given within 3 hours of delivery. The study was performed from a health care institution perspective with a time horizon of delivery until 6 weeks postpartum. We included interventions that differed by arm in the World Maternal Antifibrinolytic trial (hemorrhage-related mortality, laparotomies, and brace or compression sutures) and incorporated probabilities and costs based on available data for a population of women with postpartum hemorrhage in the United States. In our base case, the rate of postpartum hemorrhage—related mortality was 0.0388%, and the cost of tranexamic acid was $37.80. We assumed that the relative risk reduction in death and laparotomy with tranexamic acid would be similar to the World Maternal Antifibrinolytic trial (19% and 36%, respectively). The primary outcome was incremental cost per hemorrhage-related death averted, and a main secondary outcome was incremental cost per laparotomy avoided under each strategy. Another planned secondary outcome was cost per quality-adjusted life-year. We anticipated that the risk reduction (benefit) because of tranexamic acid in the United States may be less than in the World Maternal Antifibrinolytic trial; thus, we performed 1-way and 2-way sensitivity analyses to explore the parameter uncertainty across a wide range of data-supported estimates. Probabilistic sensitivity analyses with Monte Carlo simulation were performed.

RESULTS: Tranexamic acid strategies were dominant (more effective and cost saving) compared with no tranexamic acid for patients with postpartum hemorrhage in the United States. One-way analyses showed that tranexamic acid is cost saving as long as the relative risk reduction of death with tranexamic acid is greater than 4.7%; the model was not sensitive to any other variables. Threshold analyses outside the bounds defined in the model showed that tranexamic acid is cost saving as long as the relative risk reduction of laparotomy with tranexamic acid is greater than 7% or the cost of tranexamic acid is less than $194. A 2-way sensitivity analysis of the risk reduction of death because of tranexamic acid and the baseline risk of postpartum hemorrhage—related death confirmed that tranexamic acid is cost saving across a wide range of plausible estimates. Furthermore, probabilistic sensitivity analysis demonstrated that the tranexamic acid strategies are cost saving in >99.9% of 10,000 Monte Carlo simulations. Despite the initial cost of administration, the annual net cost savings expected from routine use of tranexamic acid for the treatment of postpartum hemorrhage in the United States is $11.3 million, and we estimate that 9 maternal deaths would be averted in 1 year with this strategy. Giving tranexamic acid within 3 hours would almost triple the cost savings and improve maternal outcomes much further.

CONCLUSION: A policy of routine tranexamic acid early in the treatment of postpartum hemorrhage is likely to be cost saving in the United States. This conclusion holds true even when the relative risk reduction with tranexamic acid is significantly less than reported in the World Maternal Antifibrinolytic trial and when tranexamic acid is significantly more expensive than currently reported.

Key words: cost-effectiveness, postpartum hemorrhage, tranexamic acid

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality in the United States. In 2 analyses of national inpatient samples, PPH accounted for nearly 20% of in-hospital deaths after childbirth and almost 50% of severe maternal morbidity.[1,2] Per the Centers for Disease Control and Preention National Pregnancy Mortality Surveillance System, PPH was the cause of 11% of pregnancy-related deaths in the United States from 2011 to 2015.[3]

The incidence of PPH is increasing in the United States, largely because of the increasing incidence of uterine atony.[2,4] Major obstetric hemorrhage is uncommon and unpredictable and can require the implementation of multiple nonpharmacological interventions after uterotonic administration, often concurrently: uterine balloon tamponade, uterine artery embolization (UAE), uterine compression sutures, or artery ligation, and hysterectomy. This makes the treatment process challenging to study.[5]

In response to the recognition of the hemorrhage-associated maternal morbidity and mortality, many institutions and health systems have instituted PPH protocols that include obstetric rapid response teams and massive transfusion protocols; these stepwise multidisciplinary approaches

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AJOG at a Glance

Why was this study conducted?

- The World Maternal Antifibrinolytic (WOMAN) trial showed a reduction in hemorrhage-related maternal mortality with the use of tranexamic acid.
- The cost-effectiveness of tranexamic acid in a developed country such as the United States, where the hemorrhage-related maternal mortality is lower than that reported in the WOMAN trial, has not been assessed.

Key findings

- Tranexamic acid is cost saving across a wide range of plausible scenarios.
- Tranexamic acid is cost saving as long as the relative risk reduction in hemorrhage-related mortality with tranexamic acid is greater than 4.7% (it was 19% in the WOMAN trial).

What does this study add to what is already known?

- Our findings suggest that tranexamic acid is highly likely to be cost saving when used routinely for postpartum hemorrhage in the United States.
- Tranexamic acid should be a component of hemorrhage protocols in high-resource settings.

have achieved their goals of decreasing severe maternal morbidity and mortality with mixed results.[5–7] With and without protocols, the management of major obstetric hemorrhage requires significant health resources, including blood products, multidisciplinary care, surgical intervention, and sometimes intensive care.

The role of tranexamic acid (TXA), an antifibrinolytic agent, in prevention and treatment of obstetric hemorrhage is evolving rapidly. Its benefit in reducing blood loss in orthopedic surgery and bleeding trauma patients is well documented.[8–10] In the obstetric literature, multiple small randomized controlled trials have demonstrated a reduction in blood loss with the prophylactic use of tranexamic acid at the time of cesarean delivery.[11–17]

The evidence for the therapeutic use of tranexamic acid in the setting of PPH, especially after vaginal delivery, was conflicting until the landmark World Maternal Antifibrinolytic (WOMAN) trial.[18–20] The WOMAN trial, a multicenter and multicountry double-blinded, placebo-controlled randomized clinical trial, randomized 20,060 women with a clinical diagnosis of PPH to either tranexamic acid or placebo and showed a reduction in death because of bleeding (risk ratio, 0.81), primarily when given within 3 hours of giving birth (risk ratio, 0.69).[20]

The trial also showed a decrease in laparotomy rates and an increase in brace or compression sutures in the patients who received tranexamic acid. There was no difference in the incidence of venous thromboembolism, organ failure, or sepsis between the 2 groups.

As a result of this landmark study, the American College of Obstetricians and Gynecologists and the Royal College of Obstetrics and Gynecology support the use of TXA in the management of PPH, and the World Health Organization strongly recommends early use of TXA in the treatment of PPH.[6,21,22]

Whether routine use of TXA for the treatment of patients with PPH in the United States is cost effective is not known. A previous cost-effectiveness analysis using data from the WOMAN trial demonstrated that tranexamic acid is cost effective in Nigeria and Pakistan[23]; however, the cost-effectiveness of TXA has not been evaluated in a high-resource country with lower maternal mortality rates because of PPH.

With the data the WOMAN trial have provided, the increasing incidence of PPH in the United States and the resource-intensive nature of major obstetric hemorrhage, we set forth to demonstrate the cost-effectiveness of TXA in the treatment of PPH in the United States. While other developed countries participated in the WOMAN trial, the United States did not. Thus, our secondary aim was to identify circumstances in which TXA would not be cost effective or cost saving. We hope to inform whether TXA should be universally included in PPH protocols in the United States.

Materials and Methods

Model

We constructed a decision tree using Treeage 2018 (Williamstown, MA) comparing 3 strategies in women with PPH from a health care institution perspective: no TXA, TXA given at any time, and TXA given within 3 hours of delivery. In considering these 3 strategies, our first question was whether TXA is cost effective or cost saving. Our second question was what additional benefit the administration of TXA within 3 hours could provide. We wanted to account for the possibility that the timing of TXA can be the deciding factor in whether TXA is cost saving.

For our primary analysis, we chose the perspective of the health care system, comprising the hospital and health care providers, because estimating the cost of a maternal death from that perspective appeared more concrete and reliable than estimating the cost of a maternal death from the societal perspective in which it would be almost impossible to quantify the impact on families and communities. Furthermore, this perspective is relevant with regard to making a policy decision on incorporating TXA in a hospital protocol for PPH.

The interventions that differed by arm in the WOMAN trial, hemorrhage-related mortality, laparotomies, and brace or compression sutures, were included in the model. All patients in the model had PPH requiring second-line uterotonics and were given 1 of the 3 strategies, regardless of mode of delivery. Each strategy was structured identically: patients could then undergo laparotomy

or no laparotomy, which was designated as a procedure separate from delivery; have brace sutures or no brace sutures (independent of laparotomy); and then die because of hemorrhage or not (see Supplemental Figure).

Our outcomes for the primary analysis were cost, number of laparotomies, and maternal deaths. The time horizon was childbirth to 6 weeks postpartum because that was the time that patients were followed up in the WOMAN trial.

We performed a concurrent secondary analysis from the societal perspective in which we considered quality-adjusted life-years (QALYs) and cost per QALY, which are referred to as the secondary outcomes in the following text. The time horizon for this secondary analysis was average female life expectancy in the United States.[24]

Utilities and costs were discounted at a 3% annual rate. We did not decide on a predefined cost-effectiveness threshold because there is no universally accepted threshold for the cost a country or health system is willing to pay to prevent a maternal death. If TXA were not dominant, we intended to explore a wide range of cost per maternal death thresholds with a cost-effectiveness acceptability curve.

For the base case analysis, we assumed that the relative risk reduction of TXA for death and laparotomy in our US population would be similar to the WOMAN trial. Acknowledging that the benefit of TXA may be different in health care systems with more resources, we explored a wide range of probable relative risk reductions in sensitivity analyses. Other complications and interventions that were not statistically significantly different between arms in the WOMAN trial were not included in the model.

We assumed that the likelihood of death from nonhemorrhage causes were equal in each arm, as was the case in the WOMAN and Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 trials.[8,20] We assumed that the relative risk of brace sutures for patients who received TXA within 3 hours was the same as those who received it at any point because this was not specified as being different in the WOMAN trial. Finally, we assumed that there was no interaction between our outcomes.

We incorporated probabilities and costs based on available data in the literature, adapted to best represent a population of women with PPH in the United States. Base-case estimates and ranges used in sensitivity analyses for the probabilities, costs, and utilities in this model are seen in Table 1.

Probabilities

For the estimate of hemorrhage-related mortality, we decided that the study of PPH-associated morbidity and mortality in the United States by Marshall and colleagues using the 2012−2013 national inpatient sample was the best estimate.[25] Because of the potential for error in deriving a hemorrhage-specific mortality rate from the literature with the denominator for our model being patients with obstetric hemorrhage, not total live births, we calculated a weighted 95% confidence interval from the base case estimate and then designated 10% of that to be the lower bound for the sensitivity analyses.

We used the hemorrhage-related mortality rate in the placebo group in the WOMAN trial as the upper bound because it was a clear overestimate of the hemorrhage-related mortality rate in a developed country such as the United States. We reviewed the published hemorrhage-related mortality rates in the Western world from the last 15 years to confirm these estimates fit within the bounds of our range for sensitivity analyses.

The challenge with estimating laparotomy rates in PPH is that most studies evaluate either the rate of peripartum hysterectomies for PPH, which underestimates the rate of laparotomy, or they evaluate the rate of laparotomy in massive PPH only, which overestimates the rate of laparotomy for all PPH.

We calculated a weighted average of the largest and most recent studies available; the base case estimate is thus mainly reflective of the 2 studies of peripartum hysterectomy rates in PPH using the national inpatient sample.[2,25] This means that the base case estimate is probably underestimating the laparotomy rate in PPH.

For the sensitivity analysis, we made the rate of laparotomy in the placebo group in the WOMAN trial the lower bound because the published rates of peripartum hysterectomy and laparotomy are higher in the United States and western Europe than in the WOMAN trial. We made the upper bound the rate of laparotomy in a prospective multisite case series of all patients receiving an intrauterine balloon for PPH in France.[26]

The base case estimate of the probability of brace sutures in PPH was a weighted average of 2 studies that calculated the rate of brace sutures at their institutions in France and the United States.[27,28] The lower bound for the sensitivity analysis was the rate of brace sutures in the placebo arm of the WOMAN trial, and for the upper bound, we used the higher rate of the 2 studies used in the base case.

Costs

There is no established way to estimate the cost of a maternal death from a societal or health system perspective. For this model, we added the cost of an intensive care unit (ICU) stay to the cost of malpractice for a poor obstetric outcome to obtain our base case estimate for maternal death. Because our primary analysis was performed from the health care provider perspective, we did not include the societal costs of a maternal death, such as lifetime productivity and familial interruptions. Because these costs are quite difficult to quantify, we also did not include them in the societal perspective analysis and instead accepted that the cost savings from reducing maternal death (and thus economic benefit of TXA) in our secondary analysis would be underestimated.

For our cost estimate, we averaged the calculated costs of ICU stays in US and Canadian hospitals published in 3 studies.[29−31] We averaged the following for the base case estimate of malpractice costs: average payment for claims involving a neurologically impaired

TABLE 1
Data inputs to estimate probabilities, costs, and health-state utilities

Type of input	Variable	Base case value	Range (1-way sensitivity analysis)	Sources
Probabilities[a]	Rate of laparotomy for PPH	0.0214	0.0127–0.0944	Bateman et al, 2010[2]; Laas et al, 2012[28]; Shakur et al, 2017[20]; Marshall et al, 2017[25]; Revert et al, 2017[26]
	Relative risk of laparotomy with TXA	0.6400	0.49–0.85	Shakur et al, 2017[20]
	Relative risk of laparotomy with TXA in <3 h	0.5100	0.29–0.95	Shakur et al, 2017[20]
	Rate of brace sutures for PPH	0.0557	0.0250–0.0601	Laas et al, 2012[28]; Einerson, 2015[27]
	Relative risk of brace sutures with TXA	1.1900	1.01–1.41	Shakur et al, 2017[20]
	Relative risk of brace sutures with TXA in <3 h	1.1900	1.01–1.41	Shakur et al, 2017[20]
	Rate of mortality due to PPH	0.000388	0.00001–0.019	Marshall et al, 2017[25]; Ramler, 2017[44]; Bateman et al, 2010[2]; Shakur et al, 2017[20]; Gilbert 2013[45]; Chassard, 2017[46]
	Relative risk of PPH mortality with TXA	0.81	0.65–1.0	Shakur et al, 2017[20]
	Relative risk of PPH mortality with TXA in <3 h	0.69	0.52–0.91	Shakur et al, 2017[20]
Costs[b]	Cost of laparotomy	15.097	6.900–46.126	Gilbert 2013[45]; Wymer, 2014[47]; Lim, 2018[48]; healthcare bluebook[49]
	Operating room cost per minute	0.0428	0.0197–0.0647	Bogani, 2016[50]; Cleveland Clinic[51]
	Cost of 10 min of operating room plus $10 suture	0.0438	0.207–0.657	
	Average cost of ICU stay	49.076	41.606–60.346	Zimmerman et al, 1993[29]; Khandelwal et al, 2016[30]; Fernando et al, 2018[31]
	Average malpractice payment	1072.095	418.14–1237.3	Rosenblatt and Hurst, 1989[33]; Studdert et al, 2006[34]; ACOG, 2015[52]
	Total cost for maternal death	1121.171	41.606–10,000.000	
	Cost of TXA	0.0378	0.0043–0.061	Li et al, 2018[23]; Ramkumar et al, 2018[35]; drugs.com[36]
Utilities	Short-term health state after laparotomy	0.565	0.3–0.87	Sculpher, 1998[53]; Chung, 2001[54]; Turner, 2008[55]; Fawsitt, 2013[56]; Lim, 2018[48]
	Long-term health state after laparotomy	0.909	0.5–0.96	Sculpher, 1998[53]; Chung, 2001[54]; Hurskainen, 2004[57]; Lim, 2018[48]
	Short-term health state, no laparotomy	0.653	0.3–1.0	Turner, 2008[55]; Tan, 2010[58]; Fawsitt, 2013[56]
	Long-term health state, no laparotomy	0.962	0.87–1.00	Kind, 1999[59]; Chung, 2001[54]; Culligan, 2005[60]
	Short-term health state if died	0.41	0.2–0.6	Li et al, 2018[23]
	Long-term health state if died	0	0–0.03	Xu et al, 2010[17]; Chung, 2001[54]; Mission, 2012[61]; Mankuta, 2003[62]

ICU, intensive care unit; *PPH*, postpartum hemorrhage; *TXA*, tranexamic acid.

[a] The relative risks were converted to risk differences in the model; [b] Costs in thousands of 2018 USD.

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infant from the 2015 American College of Obstetricians and Gynecologists survey on professional liability; average payment in cases in which error was found, won by plaintiff, in a review of 1452 malpractice claims from 5 insurers in the United States; and a review of 54 obstetric malpractice claims from a single insurer in the United States.[32–34]

The lower bound for the sensitivity analyses was the lowest cost of an ICU stay in the included studies with no malpractice costs, and the higher bound was 10 million USD as a feasible

payment for a malpractice suit involving a maternal death.

To estimate the costs of laparotomy, we averaged the published costs of hysterectomy and cesarean delivery, especially cesarean for uterine rupture, and used the lowest lower bound and highest higher bound in the included studies for the sensitivity analyses. We estimated the cost of brace sutures by estimating the cost of 10 minutes of operating room time based on the best studies available and adding 10 USD as the cost of a suture for a compression stitch.

We estimated the cost of 1 g of TXA by averaging the lower and upper limits of the cost range of TXA on drugs.com with other recently published estimates of the cost of TXA.[23,35–37] We did not calculate a separate cost for the administration of the drug because, in the United States, most patients being treated for PPH who have already required and received second-line uterotonics have one-to-one nursing and already have intravenous access; thus, this cost would not differ between arms in the model.

We used the same cost of TXA for the health system and societal perspectives because we were unable to find reliable estimates for the cost of the drug from a hospital perspective; we accounted for the possible difference in cost in the sensitivity analyses. We used the lower bound of the TXA cost in the Nigeria and Pakistan cost-effectiveness analysis as the lower bound for our sensitivity analysis and the cost of TXA in a recent cost-effectiveness analysis for joint replacements, in which the cost of administering the drug was included as the upper bound for our sensitivity analysis.[23,35] All costs were converted to 2018 USD using the health care component of the US price index for personal consumption expenditures.[38]

Utilities

For our secondary analysis incorporating QALYs over the patient's remaining lifetime, we assigned short-term utilities for the first 42 days after PPH and long-term utilities from then until death based on the best data available, similar to Li et al.[23] We prioritized patient-centered data and excluded measures from expert panels unless there were no other data available.

Because the median life expectancy for women in the United States is 81 years,[24] and the median age of childbirth in the United States is 29 years,[39] the median remaining life-years after PPH in the model was 52 years. For women who died, we estimated the short-term and long-term utility to be 0.

For women who survived and had a laparotomy, we estimated the short-term utility as being similar to that of the acute postoperative period after an emergent cesarean or hysterectomy for benign indications, and we estimated the long-term utility to be between that of a cesarean delivery and hysterectomy. For women who survived and did not have a laparotomy, regardless of brace sutures, we estimated the short-term utility to be between the acute utility of having had a blood transfusion and an uncomplicated cesarean delivery and the long-term utility to be that of healthy women.

Primary outcomes and sensitivity analyses

Primary outcomes included incremental cost, PPH-related deaths avoided, and laparotomies avoided under each strategy. In our secondary analysis in which we incorporated utilities, our primary outcome was the incremental cost-effectiveness ratio for each strategy (cost per QALY). We performed 1-way and 2-way sensitivity analyses on all model inputs to explore the parameter uncertainty across a wide range of data-supported estimates.

Because the risk reduction for maternal death or laparotomy with TXA in the United States may be lower than in the WOMAN trial, we focused many of our sensitivity analyses on this parameter. In the 1-way sensitivity analyses, we assumed that the relative risk of laparotomy and death were always lower if TXA was given in less than 3 hours compared with being given at all (ie, the relative risks for these outcomes were correlated in the TXA strategies).

For the probabilistic sensitivity analyses, we created distributions for each model input to match the standard deviation and distribution of data reported in the literature. We assigned gamma distributions to cost and to positive relative risk variables to represent their nonnormal right skew. For all other probabilities and variables with values between 0 and 1, we assigned beta distributions. We then performed probabilistic sensitivity analyses with Monte Carlo simulation.

Results

The TXA strategies were dominant (more effective and cost saving) compared with no routine TXA for patients with PPH in the United States, with TXA within 3 hours being the most dominant strategy (Table 2). In the base case analysis, giving TXA to women with PPH saved $11.3 million, prevented 334 laparotomies, and averted 9 maternal deaths in the United States annually, assuming 4 million births with a 3% rate of PPH.

Giving TXA within 3 hours almost tripled the cost savings and improved maternal outcomes much further. Compared with any TXA, administration of TXA within 3 hours of giving birth, when extrapolated to the US population, prevented 924 more laparotomies, 5 additional maternal deaths, and saved an additional $18.8 million in 1 year. The annual cost savings expected from routine use of TXA for early treatment of PPH in the United States was $30.1 million, with the prevention of 1258 laparotomies and 14 maternal deaths per year.

One-way threshold analyses showed that the model was sensitive to 1 variable: the risk reduction in hemorrhage-related mortality with TXA. TXA was cost saving as long as the risk reduction in hemorrhage-related mortality was greater than 4.7%. The model was otherwise not sensitive to any other variables (see Figure 1).

To further define the limits of when TXA was cost saving, we then performed threshold analyses outside the bounds defined in the model. These showed that TXA was cost saving unless the relative risk reduction of laparotomy with TXA was less than 7% or the cost of TXA was more than $194. These thresholds were

TABLE 2
Cost savings, laparotomies averted, and maternal deaths averted in the United States per year[a]

Strategy	Cost savings (2018 USD)	Laparotomies averted	Deaths averted
No TXA	0	0	0
Any TXA	11,308,283	334	9
TXA in 3 h	30,100,508	1258	14

TXA, tranexamic acid.

[a] Assuming 4 million births and 3% rate of postpartum hemorrhage.

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well outside the ranges used in the model, which were based on the best estimates available in the literature.

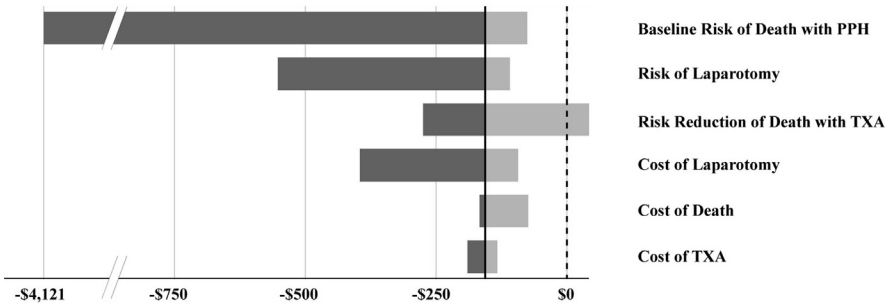
We performed a 2-way sensitivity analysis of the 1 variable that the model was sensitive to, the risk reduction of death because of TXA, and the baseline probability of PPH-related death, which was the parameter that seems to be the most different between the United States and that in the WOMAN trial. This 2-way sensitivity analysis confirmed that TXA was cost saving across a wide range of plausible estimates (see Figure 2).

A probabilistic sensitivity analysis with 10,000 Monte Carlo simulations demonstrated that the TXA strategies were cost saving in >99.9% of simulations. We performed a post hoc analysis including the administration cost of TXA in the model, and there was no difference in the primary outcome or the probabilistic sensitivity analysis.

In the secondary analysis in which we included utilities in the model, the ranking of the strategies was the same as in the primary analysis (see Supplemental Table). The model was not sensitive to variation in any of the variables in 1-way and 2-way sensitivity analyses. The Monte Carlo simulation was the same as in the primary analysis.

To explore the possibility that TXA could be much less effective in the United States, we performed a threshold analysis for the risk reduction of hemorrhage-related mortality and laparotomy, using a willingness to pay of $100,000 per QALY, the most commonly used cost-effectiveness threshold in the United States. In this analysis, the threshold for TXA to be cost-effective was a 0.05% relative risk reduction in hemorrhage-related mortality and a 0.2% relative risk reduction in laparotomy rates.

FIGURE 1
Results of sensitivity analyses comparing TXA with no TXA



Key results of 1-way sensitivity analyses comparing TXA with no TXA in cost per patient with PPH. The *bars* represent the ranges of the model inputs used in the 1-way sensitivity analyses. The *dashed vertical line* is the cost-savings threshold at $0. The *vertical line* demarcating the interface between *dark* and *light gray bars* is the base case estimate ($156.60 saved per patient with PPH who received TXA). Costs are in 2018 USD.

PPH, postpartum hemorrhage; *TXA*, tranexamic acid.

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Comment

Principal findings

This study evaluated whether TXA is likely to be cost effective in the treatment of PPH in a population of US women. We demonstrated that the routine use of TXA in the treatment of PPH is expected to be a cost-saving policy in the United States despite the upfront cost of TXA treatment.

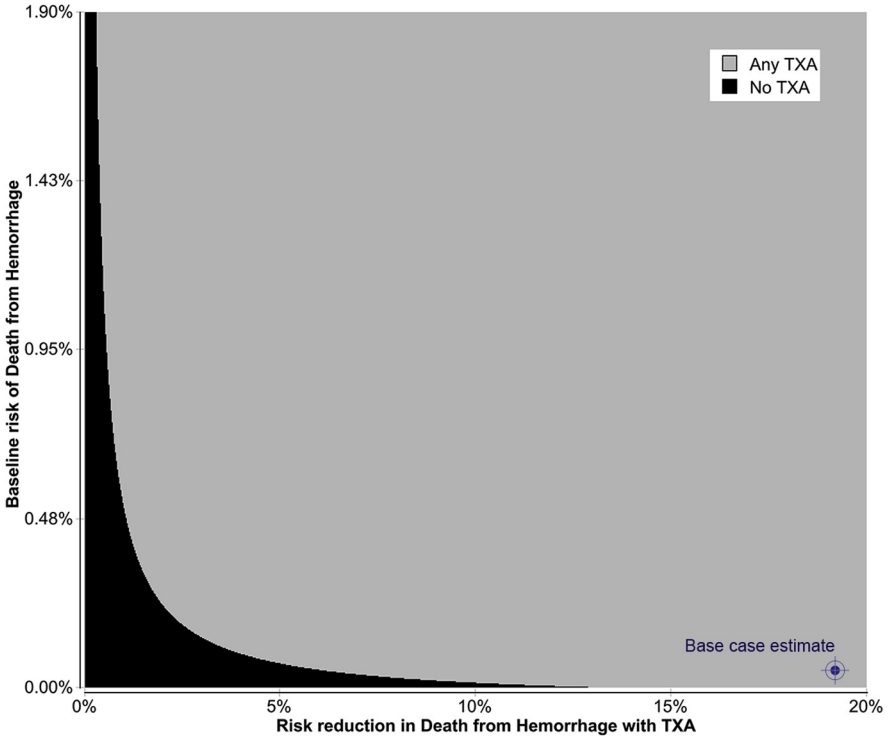
Sensitivity analyses show that this conclusion is robust across a generous range of possible probability, cost, and utility estimates. This was true whether one assumes a short-term health care system perspective or a long-term societal perspective. Furthermore, our model suggests that routine administration within 3 hours, as opposed to TXA given at any time in the treatment of PPH, is expected to achieve the greatest effect with the most cost savings and maternal benefit.

Finally, we found that TXA treatment for PPH is cost saving in the United States as long as the relative risk reduction for maternal death is greater than 5%, the relative risk reduction for laparotomy is greater than 7%, and the cost of TXA is less than $194. These circumstances are very likely to exist in most settings in the United States.

Results of the study in context

One other cost-effectiveness analysis has evaluated the use of TXA in reducing hemorrhage-related maternal mortality: the study by Li et al.[23] They used country-specific data from the WOMAN trial for Nigeria and Pakistan, which we were not able to do, because the United States was not included in the multicountry study. We did make the adjustments as noted in the previous text to tailor the model to the US context based on available literature. Our estimate of the cost of TXA was higher.

FIGURE 2
Risk of PPH-related death and risk reduction thereof with TXA



Two-way sensitivity analysis of baseline risk of death because of PPH and risk reduction in death from hemorrhage with TXA. The *light gray shaded area* depicts the combinations of these variables in which any TXA strategy is dominant, and the *black shaded area* shows the values at which no TXA is the dominant strategy. The base case estimate is represented with an icon to the *bottom right*.

PPH, postpartum hemorrhage; *TXA*, tranexamic acid.

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Our approach furthermore differed from that of the study by Li et al[23] in that our primary outcomes were cost and laparotomies and deaths averted, whereas their primary outcomes were per-patient cost and QALYs. With our comparatively lower hemorrhage-related mortality rates, higher laparotomy rates, longer life expectancy, and different perspective (that of the health care provider), the outcomes we chose seemed more impactful and relevant, especially once we found that TXA was cost saving across most scenarios.

The most significant difference between our study and that of Li et al[23] is that they addressed the developing world, while our model evaluated the cost-effectiveness in the United States, with results that could be extrapolated to similar health systems in the developed world.

As stated above, the main challenge for this study was applying the WOMAN trial to the US context. We assumed that the relative benefit of TXA in the United States would be similar to the WOMAN trial and estimated that the baseline rate of hemorrhage-related death would be much lower. We intentionally allowed for a wider range of possible risk reductions for death and laparotomy in sensitivity analyses to account for the possibility that the benefit may be different in a well-resourced health system. Our sensitivity analyses and probabilistic simulations suggest that TXA is expected to be cost saving in almost all clinical circumstances in the United States, even if the effectiveness of TXA is much less than previously reported.

For TXA to be cost effective at a willingness to pay of $100,000 per QALY, only very modest relative reductions in maternal death from hemorrhage (0.05%) or laparotomy (0.2%) with TXA are needed. If, however, TXA provides no benefit, its routine use in the treatment of PPH in the United States would add an estimated $4.5 million in health care costs per year.

Clinical implications

Our findings suggest that national guidelines in the United States should make a stronger recommendation for the use of TXA in the management of PPH. Hospitals including TXA in PPH protocols should include directions to administer TXA within 3 hours of birth and PPH onset.

The risk of venous thromboembolism with TXA is a frequently cited reason for not using the medication, but this concern is not supported by the 2 large multicenter, multinational randomized controlled trials using TXA.[8,20] In addition to these 2 landmark studies, multiple meta-analyses of randomized trials in the orthopedic literature show that there is not an increased risk of venous thromboembolism with the use of TXA.[40–42] The WOMAN trial did not exclude women at higher risk for thromboembolic events, and the rate of thromboembolic events (0.3% of 20,021 participants) was not statistically different in the 2 groups.

A limitation in the interpretation of these results from the WOMAN trial is that the patients were not followed up long term, with most outcomes being ascertained at the time of hospital discharge. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 trial with 20,211 patients is the largest randomized placebo-controlled trial using TXA and also found no difference in thrombotic events between the 2 groups.[8]

Seizures have been associated with TXA. However, this association has been reported in the use of TXA for cardiac surgery in which the doses of TXA are much higher (24–100 mg/kg) and in which the patients are generally much older than the obstetric population.[43] There was no difference in the rate of seizures between the 2 groups in the

WOMAN trial (0.3% and 0.4%). Thus, the results of the WOMAN trial along with the results of our study suggest that incorporation of TXA in hospital protocols for the treatment of PPH is warranted.

Research implications

A large clinical trial like the WOMAN trial will not be replicated in the United States, especially because the concern is that TXA may be less effective in the United States, meaning that a much larger sample size would be needed to show a difference. Thus, a cost-effectiveness analysis provides a useful means of answering the question of whether TXA is likely to be cost effective in the United States by replicating the analysis over a wide range of parameters.

Currently the data regarding the prophylactic use of TXA at the time of delivery in patients at an a priori higher risk for PPH is mixed. The ongoing Maternal-Fetal Medicine Units Network trial (NCT03364491) should answer that question for cesarean delivery in the United States. With the data of that trial, the next step from a cost perspective will be to ascertain the cost-effectiveness of prophylactic TXA at different levels of risk for PPH.

Strengths and limitations

Inherent to the validity of any cost-effectiveness analysis is the validity of the inputs. We used the best estimates available in the literature, but utilities are often imperfectly measured and real costs opaque. There is no reliable way to calculate the cost of a maternal death. A simple cost accounting of the services rendered in the care of young women who die of preventable causes is inadequate to capture the societal, psychosocial, legal, and relational cost and burden of a maternal death. In acknowledgment of this reality, we estimated the cost of maternal death from a health care perspective by adding the costs of an ICU admission and a malpractice suit. This is almost surely an underestimate of the societal cost of a maternal death. If so, we have underestimated the cost savings of TXA.

While a large randomized clinical trial is rarely available in obstetrics to provide data for a cost-effectiveness analysis, the WOMAN trial does have its limitations, which carry into our study: for example, ICU admissions were not captured, and the rate of UAE was low. ICU admissions and UAE are a significant part of the resources used in managing major obstetric hemorrhage in the United States. We therefore could not include these outcomes in our model. We hypothesize that TXA may reduce the need for these resources; if so, our model again underestimates the benefit of using TXA.

As described in the previous text, complications and interventions that were not statistically significantly different between arms in the WOMAN trial were not included in the model: transfusion, hysterectomy, use of uterotonics, venous thromboembolism, cardiac arrest, stroke, multiorgan failure, sepsis, seizure, and quality-of-life measures such as mobility, self-care, pain, and mood. Genitourinary tract injury was not reported in the WOMAN trial, and we did not include it as a complication in the model because it is usually associated with peripartum hysterectomy, which was not statistically different between arms in the WOMAN trial.

With our sensitivity analyses, we have tried to overcome the limitations in generalizing the results of the WOMAN trial to the US population. We do believe that this study is timely and relevant and that the study design has provided a platform to model the WOMAN trial in a US population while providing the ability to explore its limits.

Conclusions

In conclusion, we have shown that a policy of routine TXA administration in the treatment of major obstetric hemorrhage in the United States is expected to result in substantial cost savings and reduction in maternal morbidity and bleeding-related mortality. Sensitivity analyses showed that TXA is cost effective, even when it affords a very small benefit. Based on our results, we recommend that hospitals and obstetric care providers consider implementation of TXA in the treatment of PPH in the United States and other high-resource settings. Outcomes would be optimized if given within the first 3 hours of birth, which may be best achieved by including TXA in PPH algorithms. ■

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Author and article information

From the Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (Drs Sudhof and Shainker); and the Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Utah Health, Salt Lake City, UT (Dr Einerson).

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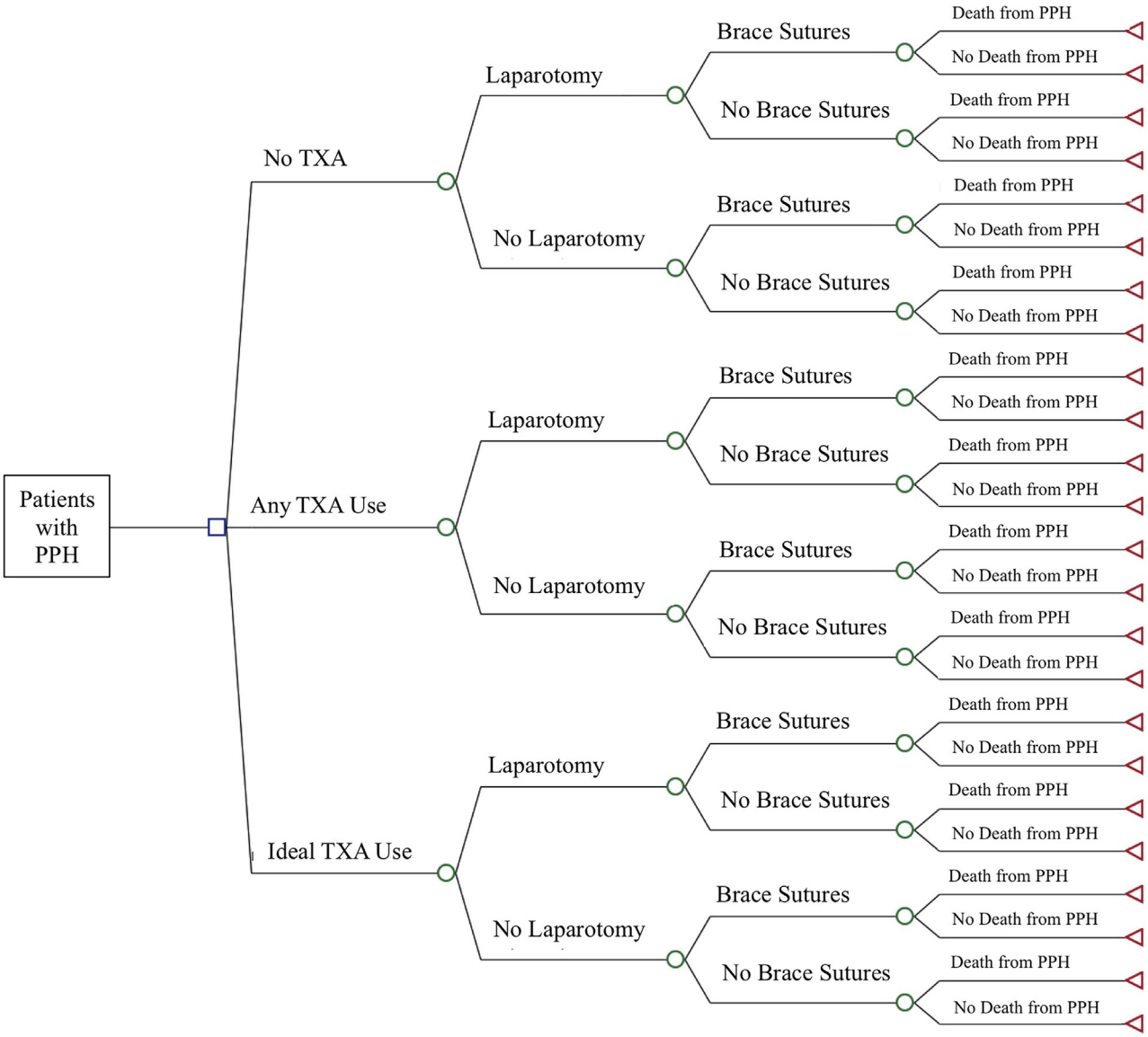
Corresponding author: Leanna Sudhof, MD. lsudhof@bidmc.harvard.edu

SUPPLEMENTAL FIGURE
Decision tree



Structure of the decision tree used to evaluate the cost-effectiveness of using TXA in the treatment of PPH.

PPH, postpartum hemorrhage; *TXA*, tranexamic acid.

Sudhof et al. Cost-effectiveness of tranexamic acid. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE

Lifetime cost-effectiveness of the 3 strategies

Strategy	Cost	Incremental cost	QALYs	Incremental QALYs	Cost per QALY	Laparotomies[a]	Brace sutures[a]	Deaths[a]
No TXA	782.77	0	50.02	0	15.65	214	557	4
Any TXA	626.17	−156.60	50.05	0.03	13.70	137	663	3
TXA <3 h	531.93	−250.84	50.06	0.01	10.91	109	663	3

QALY, quality-adjusted life-year; *TXA*, tranexamic acid.

[a] Per 10,000 women with postpartum hemorrhage.

Sudhof et al. Cost-effectiveness of tranexamic acid. Am J Obstet Gynecol 2019.