GOOD EVIDENCE MATTERS

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FPIN
Family Physicians Inquiries Network

Volume 6 Issue 8

Does a Quick Push of TXA Keep the Bleeding Away?

Tranexamic Acid to Prevent Obstetrical Hemorrhage after Cesarean Delivery

Pacheco LD, Clifton RG, Saade GR, et al. Tranexamic Acid to Prevent Obstetrical Hemorrhage after Cesarean Delivery. *N Engl J Med*. 2023;388(15):1365-1375. doi:10.1056/NEJMoa2207419

KEY TAKEAWAY: Prophylactic tranexamic acid (TXA) does not reduce occurrence of maternal death or blood transfusion compared to placebo in pregnant patients undergoing cesarean section.

STUDY DESIGN: Multicenter, double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Postpartum hemorrhage is a significant cause of maternal death, both in the United States and worldwide. TXA, a fibrinolysis inhibitor, is commonly used in treating postpartum hemorrhage, and has been proposed as potential prophylaxis of postpartum hemorrhage as well. However, the current evidence for prophylactic use at time of delivery is limited.

PATIENTS: Pregnant adults undergoing cesarean delivery

INTERVENTION: Prophylactic TXA

CONTROL: Placebo

PRIMARY OUTCOME: Composite of maternal death or blood transfusion before discharge from the hospital or seven days postpartum

Secondary Outcome: Intraoperative blood loss >1 L, composite of treatments and interventions within seven days post-partum, related complications

METHODS (BRIEF DESCRIPTION):

- Adult pregnant patients who were undergoing scheduled or unscheduled cesarean section of a singleton or twin pregnancy were eligible for the study.
- Average age at delivery was 30 years old; the majority of patients were Black or Hispanic and approximately 75% had a body mass index (BMI) >30.
- Patients with placenta previa (1.7% of patients), chorioamnionitis (3%) and twin pregnancies (4.2%) were included. Approximately half of patients had a prior cesarean delivery.
- Patients were randomized 1:1 to receive either TXA or placebo, which were given immediately after umbilical cord-clamping.
- TXA was given as 1 g (10 ml) diluted in 40 ml normal saline IV.
- Placebo was given as 50 ml normal saline IV.
- The primary outcome measured the composite of maternal death or blood transfusion (packed red blood cells or whole blood, or the use of cell-saver autotransfusion device) prior to discharge from the hospital or seven days postpartum (whichever occurred first).
- The secondary outcomes measured intraoperative blood loss >1 L, composite of treatments and interventions within seven days post-partum, and the following related complications:
  - Intervention in response to bleeding and related complications
  - Surgical or radiologic intervention
  - Open-label use of TXA
  - Transfusion of any blood product
  - Transfusion of blood products other than packed red cells
  - Blood transfusion of at least four units
  - Acute kidney injury (AKI)
  - Transfusion-associated reaction

INTERVENTION (# IN THE GROUP): 5,525

COMPARISON (# IN THE GROUP): 5,470

FOLLOW-UP PERIOD: Six weeks postpartum

RESULTS:

Primary Outcome –

- TXA did not reduce the risk of composite maternal death or blood transfusion compared to placebo (adjusted relative risk [aRR] 0.89; 95.26% CI, 0.74–1.1).

Secondary Outcome –

- The percentage of patients with estimated blood loss >1 L was similar between the TXA and placebo groups.
- TXA slightly decreased the need for additional uterotonic agents compared to placebo (relative risk [RR] 0.88; 95% CI, 0.80–0.97).

- TXA slightly decreased the need for additional intervention for bleeding by 7 days postpartum compared to placebo (RR 0.90; 95% CI, 0.82–0.97).

LIMITATIONS:

- Because the TXA was administered after the umbilical cord was clamped, the effect of pre-delivery administration is unknown.
- The trial excluded patients at very high risk for thromboembolic. Safety of TXA in these conditions has not been well studied.

Giovanna Nelson, MD
Northwest Washington FMRP
Bremerton, WA

Balancing Relief and Risk: Vaginal Estrogen Use After Breast Cancer

Vaginal Estrogen Use in Breast Cancer Survivors: A Systematic Review and Meta-Analysis of Recurrence and Mortality Risks

Beste ME, Kaunitz AM, McKinney JA, Sanchez-Ramos L. Vaginal Estrogen Use in Breast Cancer Survivors: A Systematic Review and Meta-analysis of Recurrence and Mortality Risks. *Am J Obstet Gynecol*. 2025;232(3):262-270.e1. doi: 10.1016/j.ajog.2024.10.054

KEY TAKEAWAY: Low-dose vaginal estrogen did not increase breast cancer recurrence compared to no vaginal estrogen use in breast cancer survivors with genitourinary syndrome of menopause (GSM).

STUDY DESIGN: Systematic review and meta-analysis of eight observational cohort studies (N=61,695)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to statistically significant heterogeneity observed for the primary outcome)

BRIEF BACKGROUND INFORMATION: GSM is a common condition among breast cancer survivors resulting from estrogen deprivation due to cancer treatment modalities. Local vaginal estrogen is the most effective treatment for GSM, yet its use remains controversial because of concerns regarding breast cancer recurrence or mortality. This uncertainty has led to inconsistent prescribing practices and the need for evidence clarifying its safety.

PATIENTS: Breast cancer survivors

INTERVENTION: Vaginal estrogen therapy

CONTROL: No vaginal estrogen use or nonhormonal management

PRIMARY OUTCOME: Breast cancer recurrence

Secondary Outcome: Breast cancer specific mortality, overall mortality

METHODS (BRIEF DESCRIPTION):

- A systematic review and meta-analysis were conducted and observational studies of postmenopausal breast cancer survivors treated with vaginal estrogen for GSM that reported recurrence or mortality outcomes were included in the review.
- Eight retrospective cohort studies, with mean follow-up ranging from 4.2–9.8 years were examined.
- Databases searched were Google Scholar, PubMed, EMBASE, CINAHL, NCBI, and ScienceDirect. Keywords used were vaginal estrogen, urogenital atrophy, breast neoplasm, estrogen cream, and breast carcinoma.
- Studies involving systemic hormone therapy or lacking relevant outcomes were excluded from the review.
- Low dose vaginal estrogen therapy was limited to estradiol or estriol vaginal creams, and vaginal estradiol tablets
- Exact dose, frequency, or concentration of the vaginal estrogen products were not specified; however, all were categorized as local low-dose preparations for GSM.
- Duration of use varied and was not specified.
- Breast cancer survivors not using vaginal estrogen, including individuals receiving no hormonal treatment for GSM, those receiving usual care, and survivors using non-hormonal moisturizers or lubricants when reported.
- Recurrence was assessed through medical record review, oncology follow-up documentation, and cancer registry data as reported by individual studies.
- Breast cancer specific mortality was measured using cause of death data confirming breast cancer as the primary cause.
- Overall mortality was measured using verified death records of any cause from medical records, regional databases, or national death registries.
- Two independent reviewers used the Newcastle-Ottawa Scale (NOS); scores of 7–9 indicated low risk of bias.
- Pooled odds ratios and 95% confidence intervals were calculated using a random-effects model (DerSimonian & Laird).
- I^2 statistics measured heterogeneity, and fragility indices (FI/RFI) assessed result robustness.

INTERVENTION (# IN THE GROUP): 7,966

COMPARISON (# IN THE GROUP): 53,729

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Vaginal estrogen use did not increase recurrence compared to non-use (6 studies, n=24,060; odds ratio [OR] 0.48; 95% CI, 0.23–0.98; I^2=96%).

Secondary Outcome –

- Vaginal estrogen use decreased overall mortality compared to non-use (5 studies, n=59,724; OR 0.46; 95% CI, 0.42–0.49; I^2=0%).
- There was no significant difference in breast cancer specific mortality between the two groups.

LIMITATIONS:

- Limited number of studies reduced generalizability and power.
- All included studies were observational; no randomized controlled trials were identified.
- The Newcastle-Ottawa Scale may have overestimated quality compared with stricter grading tools.
- Variability existed in estrogen formulation, dose, duration, and follow-up periods.
- Follow-up times were short or inconsistently reported in several studies.
- High heterogeneity was observed for recurrence outcomes likely due to differences in populations and study design.

Folake Adekunle, MD, MSN, WHNP-BC
UAMS Southwest FMRP
Texarkana, AR

Gene Editing in Sickle Cell Disease: Clinical Outcomes of Exagamglogene Autotemcel

Exagamglogene Autotemcel for Severe Sickle Cell Disease

Frangoul H, Locatelli F, Sharma A, et al. Exagamglogene Autotemcel for Severe Sickle Cell Disease. *N Engl J Med*. 2024;390(18):1649-1662. doi:10.1056/NEJMoa2309676

KEY TAKEAWAY: Exagamglogene Autotemcel (Exa-cel) may reduce the risk of severe sickle cell crisis episodes and the number of hospitalizations in a 12-month period.

STUDY DESIGN: Phase 3, single-group, open-label study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Sickle Cell Disease (SCD) affects approximately 100,000 individuals in the United States and an estimated one in 365 Black or African American births. Patients with severe SCD experience multiple vaso-occlusive crises (VOC) annually, leading to frequent hospitalizations and reduced quality of life. Exa-cel is a gene-editing therapy that uses clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) to modify hematopoietic stem cells, thereby reactivating fetal hemoglobin (HbF) production. Prior studies have shown that a higher level of HbF is associated with lower incidence of vaso-occlusive crises. This study evaluated the efficacy of Exa-cel in reducing episodes of severe crises and frequency of hospitalizations.

PATIENTS: Patients with SCD

INTERVENTION: Exa-cel infusion

CONTROL: Baseline

PRIMARY OUTCOME: Freedom from severe VOC for at least 12 consecutive months

Secondary Outcome: Freedom from hospitalization for severe VOC for at least 12 consecutive months, freedom from severe VOC for at least nine consecutive months, increase in total and fetal hemoglobin concentrations

METHODS (BRIEF DESCRIPTION):

- This was a prospective cohort, open-label, single arm trial study.
- Inclusion criteria were patients 12–35 years old with severe SCD who had at least two severe VOC per year despite standard therapy and were eligible for autologous stem cell transplantation.
- Severe SCD was defined as having at least two of the following events in the past two years despite supportive care with pain management and hydroxyurea: Acute pain crises requiring a medical visit or red blood cell (RBC) transfusions, acute chest syndrome, priapism lasting over two hours, or splenic sequestration.
- Exclusion criteria included patients with prior stem cell transplant, presence of a 10/10 matched related donor, significant organ dysfunction or active infection, history of significant bleeding disorder, contraindications or intolerance to plerixafor or bulsulfan, and pregnancy/lactation.
- Patients had an average age of 21 years old, 55% were male, 86% identified as Black/African American, average VOC annually was 4.1 (59% had ≥3 annually), and mean hospitalization rate was 2.7 per year with 20 inpatient days annually.
- All patients received RBC transfusions with goal to maintain sickle hemoglobin (HbS) level of <30% of total hemoglobin while keeping total Hb concentration ≤11 g/dL.
- After at least four weeks of transfusion, four patients (9%) had HbS <30% and 32 patients (73%) had total hemoglobin <11 g/dl at every assessment.
- Mobilization with plerixafor was used to release hematopoietic stem cells from the bone marrow into the bloodstream safely.
- Patients then underwent apheresis to collect CD34+ hematopoietic stem and progenitor cells for exa-cel manufacturing with use of CRISPR-Cas9.
- Participants then received myeloablative conditioning with busulfan to allow for successful engraftment before infusion of Exa-cel.
- Each patient received infusion of Exa-cel intravenously through a central line 2–7 days after busulfan conditioning.
- Outcomes were verified by an independent endpoint adjudication committee as meeting the protocol definition of severe VOC, defined as an acute pain event requiring management at a medical facility, prolonged priapism, acute chest syndrome, or splenic sequestration.
- Total hemoglobin and HbF were measured from peripheral blood samples collected from scheduled

visits and mean values were calculated across patients at each time point.

INTERVENTION (# IN THE GROUP): 44

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 19 months

RESULTS:

Primary Outcome –

- In the primary efficacy set, 29 patients were free from severe VOC for at least 12 consecutive months (n=30; 97%; 95% CI, 83–100), mean VOC-free period was 22 months (range 15–46), and 93% of patients remained free from VOC at data-cutoff.

Secondary Outcome –

- All 30 patients (n=30; 100%; 95% CI, 88–100) had no hospitalizations for severe VOC for at least 12 consecutive months.
- 31 patients in the early efficacy population were free from severe VOC for at least nine consecutive months (n=32; 97%; 95% CI, 84–100).
- Among all the 44 patients, mean hemoglobin was 12±1.5 g/dL at three months, 13±1.8 g/dL at six months and sustained at normal/near-normal levels thereafter.
- The mean fetal hemoglobin was 37%±9.0% at three months, 44%±8.6% at six months, and ≥40% in all patients at follow-up.

LIMITATIONS:

- Small sample size may limit generalizability
- The follow-up was limited (median 19 months); thus, long-term durability and safety are still unknown.
- Out of 44 patients who received exa-cel infusion, only 30 had been followed for at least 16 months after infusion to be assessed for the primary outcome.
- The therapy required busulfan-based myeloablation, which poses significant risks including hematologic toxicities and infections, such as stomatitis, febrile neutropenia, thrombocytopenia and decreased appetite.

Olusayo Oketokun, MD
Central Michigan University College FMRP
Saginaw, MI

Does Private Equity Belong in Healthcare? Patients Suffer When We Prioritize Profits

Evaluating Trends in Private Equity Ownership and Impacts on Health Outcomes, Costs, and Quality: Systematic Review

Borsa A, Bejarano G, Ellen M, Bruch JD. Evaluating Trends in Private Equity Ownership and Impacts on Health Outcomes, Costs, and Quality: Systematic Review. *BMJ*. 2023;382:e075244. Published 2023 Jul 19. doi:10.1136/bmj-2023-075244

KEY TAKEAWAY: The acceleration of private equity (PE) acquisition in healthcare is pervasive across a variety of healthcare settings, particularly within the United States (US), and PE ownership is generally associated with increased costs to payers, mixed-to-negative impacts on healthcare quality, and mixed impacts on health outcomes.

STUDY DESIGN: Systematic review of 55 studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high risk of bias in included studies, quality of individual studies, and lack of meta-analysis)

BRIEF BACKGROUND INFORMATION: Healthcare entities have seen a significant rise in PE acquisition since 2000, especially within the US. PE firms acquire and consolidate companies with the intent of selling them within 3–5 years for significant profit. PE firms provide direct managerial oversight and influence administrative changes with the intent of increasing profit. This review assessed studies of the impacts of PE practices on patient safety, healthcare debt, access to care, and quality of care. The body of literature examining PE ownership in healthcare is slowly emerging, and this study is one of few academic investigations systematically evaluating PE in healthcare.

PATIENTS: Healthcare operators, mostly US-based, including nursing homes, hospitals, surgical centers, various clinics, and hospices.

INTERVENTION: PE acquisition and ownership

CONTROL: Non-PE healthcare operators/settings

PRIMARY OUTCOME: Cost to payer, quality of care, and health outcomes

Secondary Outcome: Prevalence of PE ownership of healthcare entities

METHODS (BRIEF DESCRIPTION):

- A systematic review included studies that contained empiric research on PE ownership of healthcare operators, were published in English between 2000–2023, and addressed the primary or secondary outcome measures.
  - Any study design in any country could be eligible for inclusion.
  - Primary outcomes included health outcomes, costs to patients/payers, costs to operators, and quality.
  - Secondary outcomes included prevalence of PE ownership.
- Studies were excluded if they focused on non-operator healthcare settings (e.g. laboratories, device companies).
- Of the 1,778 publications derived from electronic database searches, 55 records were ultimately included for review; 31 of these studies were quantitative.
  - The US was the most common country in included publications (n=47).
  - Nursing homes were the most assessed healthcare setting (n=17), followed by hospitals (n=9) and specialty clinics (i.e. dermatology, ophthalmology).
- Intervention: Ownership/acquisition of healthcare operator via outright purchase or majority-ownership by PE firm or brought under the control of a PE-backed platform company or management group.
- Control: Healthcare operators not acquired or owned by PE firm.
- The primary outcome assessed the following:
  - Quality of care was measured by patient satisfaction ratings, daily functioning scores, staffing of lower skilled clinicians, nursing skill mix, and appointment availability for patients receiving Medicaid.
  - Cost to patient/payer was measured by inpatient admissions, emergency department (ED) visits, and negotiated prices between hospitals and private insurers.

- Health outcomes were measured by in-hospital mortality, 30-day and 90-day mortality, COVID-19 outbreak amongst staff and/or residents, inpatient stay duration, ED visits, unplanned hospital admissions, and fertility outcomes.
- The secondary outcomes included prevalence of PE ownership or acquisition of healthcare entities via outright purchase or majority buyout by PE firm.
- Included quantitative studies underwent assessment for bias:
  - Domains were rated as either low, moderate, serious, or critical risk of bias.
- Included publications were examined for statistically significant associations ($P \leq 0.05$), which were then categorized per the author's interpretations of those findings.
  - Each category of primary and secondary outcomes on PE ownership was qualitatively ascribed a value of "beneficial," "harmful," "mixed," or "neutral."

INTERVENTION (# IN THE GROUP): Not available
COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 23 years

RESULTS:

Primary Outcome –

- Private equity ownership of a healthcare operator decreased quality of care compared to non-PE owned healthcare operators (n=27; no pooled statistical analysis completed).
  - The strength of this association was weakened in sub-analysis of only studies with moderate risk of bias.
- With moderate risk of bias, studies consistently demonstrated that private equity acquisition increased cost to payer compared to non-PE-owned healthcare operators (n=12; no pooled statistical analysis completed).
  - Notably, this included indirect mechanisms including spillover effects into local markets and concentrations of market power due to PE acquisition.
- No definitive conclusions could be drawn about the impact of private equity ownership of healthcare operators on health outcomes due to limited volume of studies and serious or critical risks of bias (n=8).

Secondary Outcome –

- Studies demonstrated a substantial rise in PE acquisition trends in healthcare settings over the past 15 years.
  - This trend spanned geographic location within the US, with notable increases in the regional Northeast and South, especially Florida and Texas.
  - This trend spanned practice settings including nursing homes, dermatology care centers, and urology care centers.

LIMITATIONS:

- 19 studies had moderate overall risk of bias, nine had serious risk, and three had critical risk of bias. The most significant form of bias was confounding.
- Given the relatively nascent nature of the subject material, the reported results lack the nuance and depth of a study that is sufficiently powered and not dependent on literature that is still in its infancy.
- The systematic review did not distinguish between subtypes of PE ownership (e.g. minority vs majority stakes).
- Relevant domains of PE acquisitions were not assessed including profitability, debt, risk of bankruptcy, productivity, organizational stability, and overall access to care.
- There was limited specificity due to classification of outcome measures into one of four impact categories.
- The generalizability of study findings to PE healthcare ownership outside of the US is limited.

Imshan Dhrolia, MD, MPH
University of Chicago Medicine/Endeavor-Northshore
Chicago, IL