GOOD EVIDENCE MATTERS

GEMs of the Week

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Saving Lives in Trauma: The Game-Changing Evidence for Tranexamic Acid

Tranexamic Acid for Traumatic Injury in the Emergency Setting: A Systematic Review and Bias-Adjusted Meta-Analysis of Randomized Controlled Trials

Fouche PF, Stein C, Nichols M, et al. Tranexamic Acid for Traumatic Injury in the Emergency Setting: A Systematic Review and Bias-Adjusted Meta-Analysis of Randomized Controlled Trials. *Ann Emerg Med*. 2024;83(5):435-445. doi:10.1016/j.annemergmed.2023.10.004

KEY TAKEAWAY: Tranexamic acid (TXA) reduces mortality at one month in patients with traumatic injuries when administered promptly in emergency settings.

STUDY DESIGN: Systematic review and bias-adjusted meta-analysis of seven randomized controlled trials (RTCs),(N=32,832)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Traumatic injury is a leading cause of death and disability with approximately 4.4 million deaths worldwide each year, making nearly 8% of the total global mortality rate. TXA an antifibrinolytic agent, has emerged as a critical intervention to mitigate bleeding and improve outcomes in trauma patients. By inhibiting plasminogen activation and fibrinolysis, TXA stabilizes blood clots and reduces hemorrhage. This study evaluated the effectiveness of TXA in traumatic injury within emergency settings.

PATIENTS: Trauma patients in emergency settings with or at risk of significant bleeding

INTERVENTION: TXA administration

CONTROL: Usual care or placebo

PRIMARY OUTCOME: One-month mortality

Secondary Outcome: 24-hr mortality, vascular occlusive events at one month

METHODS (BRIEF DESCRIPTION):

- Randomized controlled trials comparing TXA to placebo or standard care and had adult trauma patients in emergency settings with or at risk of significant bleeding were included in the review.
- Non-randomized studies, studies without relevant outcomes (mortality or vascular events), and studies involving non-trauma indications for TXA were excluded from the review.
- In the emergency setting, patients received TXA administration (1 g bolus, and mostly 1 g infusion thereafter) within three hours or placebo.
- The primary outcome assessed mortality defined as the number of patients who received a trial drug and died at 28 or 30 days.
- The secondary outcomes assessed mortality at 24 hours and vascular occlusive events at one month which included myocardial infarction (MI), stroke, deep venous thrombosis (DVT), and pulmonary embolism (PE).
- A subgroup analysis was done to analyze the following:
  - Traumatic brain injury versus all other trauma
  - Out-of-hospital vs in-hospital administration of TXA
- The credibility of each randomized controlled trial was quantified by assessing its methodological quality using the MASTER scale in order to determine the relative probability.

INTERVENTION (# IN THE GROUP): 16,645

COMPARISON (# IN THE GROUP): 16,187

FOLLOW-UP PERIOD: One month

RESULTS:

Primary Outcome –

- TXA decreased mortality at one month compared to placebo (7 trials, n=32,832; odds ratio [OR] 0.89; 95% CI, 0.84–0.95; I^2=23%; number needed to treat [NNT]=61).

Secondary Outcome –

- TXA reduced 24-hour mortality compared to control (4 trials, n=11,559; OR 0.76; 95% CI, 0.65–0.88; I^2=0%).
- There was no significant increase in vascular occlusive events.
- According to the subgroup analysis, TXA reduced mortality at one month compared to control in out-of-hospital settings (3 trials, n=3,169; OR 0.78; 95% CI, 0.64–0.95; I^2=0%; NNT=33).
- There were no significant differences in the other subgroup analyses for TXA compared to control.

LIMITATIONS:

- The review was limited by the inability to aggregate patient-centered outcomes, such as favorable neurological reports, due to inconsistent or absent reporting in the included trials.

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The Battle for Diabetes Control in Pregnancy: Oral Glucose Lowering Medications vs Insulin

Oral Glucose-Lowering Agents vs Insulin for Gestational Diabetes: A Randomized Clinical Trial

Rademaker D, de Wit L, Duijnhoven RG, et al. Oral Glucose-Lowering Agents vs Insulin for Gestational Diabetes: A Randomized Clinical Trial. *JAMA*. 2025;333(6):470-478. doi:10.1001/jama.2024.23410

KEY TAKEAWAY: For pregnant patients with gestational diabetes mellitus type 2 (GDMA2) inadequately controlled with lifestyle modifications, treatment with oral metformin and glyburide does not increase the risk of infants born large for gestational age (LGA) compared to insulin alone.

STUDY DESIGN: Multicenter, open label noninferiority, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: While insulin has been the mainstay of treatment for GDMA2, it requires daily injections that are burdensome and costly. Alternatively, metformin and glyburide are oral medications commonly used to treat type 2 diabetes; however, they are not as well studied for management of GDMA2. This study aimed to determine whether oral glucose lowering medications increase the risk of infants born LGA compared to insulin alone.

PATIENTS: Pregnant women with GDMA2 and singleton pregnancies 16–34 weeks gestation

INTERVENTION: Metformin ± glyburide if glycemic control was not achieved with metformin alone

CONTROL: Insulin

PRIMARY OUTCOME: Infants born LGA

Secondary Outcome: Maternal hypoglycemia, cesarean delivery, pregnancy induced hypertension (HTN), pre-eclampsia, maternal weight gain, preterm delivery, birth injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, neonatal intensive care unit (NICU) admission

METHODS (BRIEF DESCRIPTION):

- This study was conducted across 25 medical centers in the Netherlands.
- Pregnant women with gestational diabetes and singleton pregnancies 16–34 weeks gestation with insufficient glycemic control after two weeks of dietary changes based on lab results (fasting glucose >95, 1 hour post-prandial glucose >140, 2 hour post-prandial glucose >120), >18 years old, and understood English or Dutch were included in the study.
- Patients with pre-pregnancy diabetes, severe psychiatric or medical comorbidities, serious liver or kidney disease, current fetus with major congenital or chromosomal abnormalities were excluded from the study.
- Participants were randomly assigned 1:1 using computerized system to either metformin ± glyburide or insulin.
    - In the intervention group, oral metformin started at 500 mg daily and was up titrated to 1,000 mg twice daily or highest dose tolerated.
    - If glycemic control was not achieved, oral glyburide at 2.5 mg daily was added with dose increase up to maximum of 5 mg three times daily.
    - If glycemic control was still not achieved, subcutaneous insulin was started in lieu of glyburide while continuing metformin. Insulin was prescribed according to local practice in both long and short acting formulations in incremental doses until glycemic goals were met.
    - In the control group, both long and short acting insulin were prescribed according to local practice in incremental doses until glycemic goals were met.
- The primary outcome assessed infants who were LGA, defined as a birth weight >90th percentile.
- The secondary outcomes assessed the rates of maternal hypoglycemia, cesarean delivery, pregnancy induced HTN, pre-eclampsia, maternal weight gain, preterm delivery, birth injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, and NICU admission between the two groups.
- Intention-to-treat analysis and per-protocol analysis were performed for primary outcome measures.
- Secondary outcomes were assessed with per-protocol analysis.

INTERVENTION (# IN THE GROUP):

- Metformin only: 224

- Metformin + glyburide: 96
- Metformin with insulin or insulin alone: 31

COMPARISON (# IN THE GROUP): 401

FOLLOW-UP PERIOD: Up to six weeks post-partum

RESULTS:

Primary Outcome –

- Oral glucose-lowering medications did not increase the risk of infants born LGA compared to insulin alone (absolute risk difference 4%; 95% CI, –1.7 to 9.8%).

Secondary Outcome –

- Oral glucose-lowering medication increased the risk of maternal hypoglycemia compared to insulin alone (absolute risk difference 10%; 95% CI, 3.7–21%).
- Oral glucose-lowering medication did not affect the risk of cesarean delivery, pregnancy induced HTN, pre-eclampsia, maternal weight gain, preterm delivery, birth injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, or NICU admission compared to insulin alone.

LIMITATIONS:

- An open-label trial without blinding can impact treatment assignment, patient adherence, and outcome analysis. However, the researchers were limited to this given that it would not be possible to blindly prescribe insulin.
- Data collection, whether through chart review or patient self-report, was unclear there increases the risk of recall bias given reliance on recollection during pregnancy and at delivery.
- Long-term neonatal outcomes from treatment options, such as metformin and glyburide, which are known to cross the placenta, were not captured in this study.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Shed Pounds, Gain Life: Weight Loss May Top Testosterone for Men with Prediabetes

Testosterone Treatment, Weight Loss, and Health-Related Quality of Life and Psychosocial Function in Men: A 2-Year Randomized Controlled Trial

Grossmann M, Robledo KP, Daniel M, et al. Testosterone Treatment, Weight Loss, and Health-related Quality of Life and Psychosocial Function in Men: A 2-year Randomized Controlled Trial. *J Clin Endocrinol Metab*. 2024;109(8):2019-2028. doi:10.1210/clinem/dgae085

KEY TAKEAWAY: Weight loss may be associated with improved quality of life, regardless of testosterone supplementation in men with low testosterone and high risk for type 2 diabetes mellitus (T2DM).

STUDY DESIGN: Double-blind, placebo-controlled, randomized control trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high rate of participant dropout)

BRIEF BACKGROUND INFORMATION: Low testosterone is common in men who are at high risk of developing T2DM. In this patient population, few studies have examined the effects of testosterone treatment on quality of life and how quality of life impacts weight loss and glycemic outcomes.

PATIENTS: Men 50–74 years old

INTERVENTION: Intramuscular (IM) testosterone

CONTROL: Placebo

PRIMARY OUTCOME: Health-related quality of life (HRQoL) and psychosocial function

Secondary Outcome: HRQoL association with glycemic control, weight loss, and waist circumference

METHODS (BRIEF DESCRIPTION):

- This study analyzed mood and quality of life questionnaire results from a previous Australian trial titled, "Testosterone for Type 2 Diabetes Mellitus (T4DM)." The T4DM trial primarily evaluated the effects of testosterone treatment plus lifestyle intervention on diabetes risk.
- Eligible participants were males with impaired glucose tolerance (fasting glucose 100–125 mg/dL or 2-hour postprandial glucose 140–199 mg/dL), newly diagnosed T2DM (A1C ≥6.5%, fasting glucose ≥126 mg/dL, or 2-hour postprandial glucose ≥200 mg/dL), waist circumference of ≥95 cm (37.4 inches), and a fasting total testosterone of ≤14 nmol/L (403 ng/dL).
- Patients were excluded if they had testosterone therapy in the last year, had a hypothalamic-pituitary-testicular pathology, or had a history of androgen abuse.
- At baseline, men were an average of 60 years old, the majority had prediabetes, 20% of participants in both groups had T2DM and average testosterone was 13.9 nmol/L in the control and 13.6 nmol/L in the intervention group.
- The intervention group received 1000 mg of IM testosterone undecanoate every three months while the control group received a placebo.
    - Both groups received access to a lifestyle intervention program (Weight Watchers).
- HRQoL and psychosocial functions were measured using the following five validated self-reported scales:
    - Physical and mental health was assessed using the Short Form Survey-12 (SF-12). Scores range from 0–100, with scores >50 indicating better well-being.
    - The MacArthur Scale of Subjective Social Status (MAC) was used to measure participants perceived social status compared to their local community (MAC1) and society at large (MAC2). Scores range from 1–10 with scores >5 indicating a higher perceived social status.
    - Patient's sense of control over their lives was assessed using the Pearlin Personal Mastery Score (Mastery). Scores range from 7–28 with higher scores indicating a stronger sense of control.
    - The Sense of Coherence (SOC) assessment scores a patient's attitude towards their life and health. Scores range from 13–91, with higher scores indicating a higher sense of coherence/confidence.
    - General depression symptoms were assessed using the Center for Epidemiological Studies-Depression (CES-D) Questionnaire. Scores range from 0–60 with higher scores indicating a greater degree of depression.

- The patients completed the CES-D at baseline, week 54, and week 102 only. The other questionnaires were completed in the baseline, weeks 30, 54, 78, and 102.
- Weight loss and waist circumference were measured at weeks 30, 54, 78, and 102.
- The association of HRQoL and glycemic control was determined using a glucose measurement after two hours and the change in two-hour glucose levels from baseline via an oral glucose tolerance test (OGTT).
- The time interval for glucose measurements was not available.

INTERVENTION (# IN THE GROUP): 329
COMPARISON (# IN THE GROUP): 319

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- IM testosterone did not significantly improve quality of life in the following areas compared to placebo:
  - Physical well-being (*P*=.88)
  - Mental well-being (*P*=.79)
  - Societal perception (*P*=.23)
  - Sense of control (*P*=.20)
  - Depression symptoms (*P*=.22)
- IM testosterone improved quality of life in the following areas compared to placebo:
  - Patient perception towards their health (*P*=.03)
  - Patient self-ranking relative to others (*P*=.04)

Secondary Outcome –

- There was no association between HRQoL and glycemic control in both groups.
- Weight loss was associated with improved:
  - Mental well-being (*P*<.001)
  - Patient self-ranking relative to others (*P*=.003)
  - Sense of control (*P*=.02)
- A one-point improvement in patients baseline health perception scores were associated with weight loss for all treatment groups (–0.05 kg; 95% CI, –0.10 to –0.1).
- A one-point increase in baseline depression scores was associated with weight gain for all treatment groups (0.11 kg; 95% CI, 0.10–0.20).
- Waist circumference changes were associated with improved:
  - Mental well-being (*P*=.04)
  - Patient self-ranking relative to others (*P*=.02)
  - Social perception (*P*=.03)
- A one-point improvement in baseline physical well-being scores were associated with decreased waist circumference for all treatment groups (–0.05 cm; 95% CI, –0.10 to –0.01).
- A one-point improvement in baseline depression scores were associated with increased waist circumference for all treatment groups (0.11 cm; 95% CI, 0.02–0.20).

LIMITATIONS:

- P-values were reported without the corresponding group data, limiting the ability to interpret the magnitude and direction of the effect.
- The primary outcome was measured by self-reported scales.
- The participants were selected by the risk of diabetes and low testosterone, not based on baseline HRQoL measures.
- There was a 36% dropout rate by the end of the study.

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Teen Concussions of the Future: Biomarkers May Eventually Help Guide Diagnosis and Return to Play

Plasma Biomarkers of Traumatic Brain Injury in Adolescents with Sport-Related Concussion

Tabor JB, Penner LC, Galarneau JM, et al. Plasma Biomarkers of Traumatic Brain Injury in Adolescents With Sport-Related Concussion. *JAMA Netw Open*. 2024;7(9):e2431959. Published 2024 Sep 3. doi:10.1001/jamanetworkopen.2024.31959

KEY TAKEAWAY: Correlations between biomarker levels and sport-related concussion (SRC) symptoms may guide diagnosis and monitoring of SRC, including return to play (RTP) for adolescent athletes. Plasma glial fibrillary acidic protein (GFAP) and ubiquitin c-terminal hydrolase-L1 (UCH-L1) levels increase after SRC while total tau (t-tau) levels decrease. These levels return to normal as concussions resolve.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to disease-oriented outcomes)

BRIEF BACKGROUND INFORMATION: Rates of SRC are increasing among adolescents, with prolonged symptoms and recovery impacting daily life, especially because the developing brain may be more vulnerable. More research is needed into rapid and accurate SRC diagnosis to direct appropriate treatment. This study evaluated whether levels of four plasma biomarkers correlated with SRC symptom duration and RTP.

PATIENTS: Adolescents with SRC

INTERVENTION: Plasma biomarkers

CONTROL: Uninjured adolescents

PRIMARY OUTCOME: Change in plasma biomarkers

Secondary Outcome: Plasma biomarker levels associated with SRC symptom scores, time to RTP

METHODS (BRIEF DESCRIPTION):

- Investigators enrolled a convenience sample of Canadian adolescents 10–18 years old participating in high-risk sports including ice hockey, football, and rugby.
  - Athletes with SRC were 51% male with a median age 16 years old.
- Exclusion criteria comprised of medical conditions affecting anticipated sports participation (systemic disease, severe and/or chronic neurologic conditions, or recent surgery and/or fractures in the past 12 months).
- 216 members of the uninjured group and 80 members of the SRC group had a prior history of at least one concussion.
- All participants completed baseline assessments, including biomarker levels and a Sport Concussion Assessment Tool, 5th Edition symptom score (SCAT5). Scores ranged from 0–30 with higher scores indicating worse concussion symptoms.
- Investigators measured four plasma biomarkers: GFAP, UCH-L), neurofilament light (NfL), and t-tau levels.
- Investigators evaluated clinical symptoms with SCAT5 scores in participants who developed SRC at or before 72 hours, one week, and then every two weeks until medically cleared to RTP.
- Investigators also drew blood samples for biomarkers at most of those intervals (investigators calculated SCAT5 scores at each interval but only analyzed them if they drew biomarker levels on that day).
- A study physician confirmed SRC diagnosis and RTP in accordance with Berlin 2016 Concussion in Sport Group 5th Consensus Statement.
- Investigators examined post-SRC samples for associations between biomarker levels and severity scores.
- A statistical analysis was completed for post-SRC groups at four post injury day (PID) intervals: 0–3 days, 4–10 days, 11–28 days, and >28 days. A multilevel multivariable linear regression model was used to assess group-level differences between uninjured and post-SRC biomarker levels, adjusted for age and sex.

INTERVENTION (# IN THE GROUP): 154

COMPARISON (# IN THE GROUP): 695

FOLLOW-UP PERIOD: >28 days

RESULTS:

Primary Outcome –

- GFAP levels rose in female athletes with SRC compared to uninjured females at three time points:

- PID 0–3 (effect size 18%, β=0.16; 95% CI, 0.064–0.26)
- PID 4–10 (effect size 11%, β=0.10; 95% CI, 0.016–0.19)
- PID 11–28 (effect size 15%, β=0.14; 95% CI, 0.057–0.23)

- GFAP levels did not increase in female athletes at PID >28 compared to uninjured athletes (effect size 7.4, β=0.071; 95% CI, –0.012 to 0.16).
- GFAP levels rose in male athletes with SRC compared to uninjured males at four time points:
  - PID 0–3 (effect size 17%, β=0.16; 95% CI, 0.086–0.23)
  - PID 4–10 (effect size 12%, β=0.11; 95% CI, 0.058–0.17)
  - PID 11–28 (effect size 15%, β=0.14; 95% CI, 0.078–0.19)
  - PID >28 (effect size 11%, β=0.10; 95% CI, 0.029–0.30)
- UCH-L1 levels rose in female athletes with SRC compared to uninjured females at four time points:
  - PID 0–3 (effect size 43%, β=0.36; 95% CI, 0.13–0.60)
  - PID 4–10 (effect size 24%, β=0.21; 95% CI, 0.026–0.40)
  - PID 11–28 (effect size 33%, β=0.29; 95% CI, 0.11–0.47)
  - PID >28 (effect size 53%, β=0.42; 95% CI, 0.24 – 0.61)
- UCH-L1 did not rise significantly in male athletes with SRC compared to uninjured males at any time point.
  - PID 0–3 (effect size 12%, β=0.11; 95% CI, −0.083 to 0.30)
  - PID 4–1 (effect size 11%, β=0.11; 95% CI, −0.04 to 0.25)
  - PID 11–28 (effect size 2.1%, β=0.021; 95% CI, −0.13 to 0.17)
  - PID >28 (effect size 19%, β=0.18; 95% CI, −0.01 to 0.36)
- NfL levels did not change significantly in female athletes with SRC compared to uninjured females.
  - PID 0–3 (effect size 4.4%, β=0.043; 95% CI, −0.073 to 0.16)
  - PID 4–10 (effect size 5%, β=0.049; 95% CI, −0.05 to 0.15)
  - PID 11–28 (effect size 5.5%, β=0.053; 95% CI, −0.042 to 0.15)
  - PID >28 (effect size −2.7%, β=−0.028; 95% CI, −0.12 to 0.068)
- NfL levels rose in male athletes with SRC compared to uninjured males at two time points:
  - PID 0–3 (effect size 19%, β=0.17; 95% CI, 0.087–0.26)
  - PID 4–10 (effect size 12%, β=0.11; 95% CI, 0.043–0.18)
- NfL levels did not increase in male athletes with SRC compared to uninjured males at two time points:
  - PID 11–28 (effect size 6.3%, β=0.061; 95% CI, −0.007 to 0.13)
  - PID >28 (effect size 6.3%, β=0.061; 95% CI, −0.025 to 0.15)
- T-Tau levels decreased in female athletes with SRC compared to uninjured females at four time points:
  - PID 0–3 (effect size –23%, β=–0.26; 95% CI, –0.39 to –0.13)
  - PID 4–10 (effect size –21%, β=–0.24; 95% CI, –0.35 to –0.13)
  - PID 11–28 (effect size –15%, β=–0.16; 95% CI, –0.27 to –0.05)
  - PID >28 (effect size –2.7%, β=–0.20; 95% CI, –0.30 to –0.087)
- T-tau levels decreased in male athletes with SRC compared to uninjured males at two time points:
  - PID 0–3 (effect size –18%, β=–0.203; 95% CI, –0.3 to –0.11)
  - PID 4–10 (effect size –8.0%, β=–0.083; 95% CI, –0.16 to –0.009)
- T-tau levels increased in male athletes with SRC compared to uninjured males at PID 11–28 (effect size 9.1%, β=0.087; 95% CI, 0.011–0.16).

Secondary Outcome –

- Elevated biomarker levels post SRC were associated with higher SCAT5 symptom severity scores for the following points:
  - GFAP at PID 0–3 (effect size 0.15%, β=0.002; 95% CI, 0.001–0.003)

    - NfL at PID 0–3 (effect size 0.24%, β=0.002; 95% CI, 0.001–0.003)
    - NfL at PID 4–10 (effect 0.62%, β=0.006; 95% CI, 0.003–0.010)
- Decreased t-tau levels post SRC were associated with SCAT5 symptom severity scores at three time points:
    - PID 0–3 (effect size –0.33%, β=–0.003; 95% CI, –0.005 to –0.002)
    - PID 4–10 (effect size –0.20%, β=–0.002; 95% CI –0.003 to 0.00)
    - PID >28 (effect size 0.78%, β=0.08; 95% CI 0.003–0.012)
- Higher GFAP levels post SRC at PID >28 days were associated with a reduced time to RTP (hazard ratio [HR] 4.8; 95% CI, 1.6–14).
- No other biomarker levels at any time point were significantly associated with differences in time to RTP.

LIMITATIONS:

- The clinical insignificance of the association between biomarkers and symptoms burden was limited.
- This study might have decreased detection because investigators collected initial post-SRC samples beyond the possible 24–48 hour peak in biomarkers.
- Most participants were 15–17 years old; therefore, this study may not reflect biomarker differences in younger participants.
- Blood and cerebrospinal fluid t-tau levels are poorly correlated, and the authors report that t-tau data conclusions must be interpreted with caution.
- This study did not exclude patients with repeated concussions and did not select participants with first time concussions.
- A study physician independently confirmed SRC diagnosis and RTP but was not blinded from study data.

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