GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 4 - Issue 12

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 18 - 22, 2024

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Worry About VTE with Testosterone Replacement Therapy?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Testosterone Replacement Therapy and the Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Ayele HT, Brunetti VC, Renoux C, Tagalakis V, Filion KB. Testosterone replacement therapy and the risk of venous thromboembolism: A systematic review and meta-analysis of randomized controlled trials. *Thromb Res.* 2021;199:123-131. doi:10.1016/j.thromres.2020.12.029

KEY TAKEAWAY: Testosterone replacement therapy (TRT) does not increase the risk of venous thromboembolism (VTE) in males compared to placebo or active comparator.

STUDY DESIGN: Systematic review and meta-analysis of 13 randomized control trials (N=5,050)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Testosterone replacement therapy, a once popular treatment, has declined due to research indicating an increased arterial thrombosis risk. However, the use of TRT and the risk of venous thromboembolism is not as clear.

PATIENTS: Males ≥18 years old

INTERVENTION: TRT

CONTROL: Placebo or active comparator

PRIMARY OUTCOME: Incidence of venous thromboembolism events

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria:
  - Males on TRT (mean age ranges from 52–74 years old)
  - Reported VTE as either a primary or secondary outcome
  - Sample size >100
- TRT was defined as any testosterone replacement available on the market. Doses ranged from 5–1000 mg.
- VTE events were defined by each study, events including deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Random effects models with inverse variance weighting were used to provide relative risk across the studies.

INTERVENTION (# IN THE GROUP): 2,636

COMPARISON (# IN THE GROUP): 2,414

FOLLOW-UP PERIOD: 3–36 months

RESULTS:

Primary Outcome –

- There was no difference in the risk of the following when comparing men treated with TRT compared to men treated with placebo or active comparator:
  - VTE incidence (15/2,636 vs 12/2,414; weighted risk ratio [RR] 1.0; 95% CI, 0.49–2.1; unweighted NNH 1,391)
  - DVT (RR 1.1; 95% CI, 0.46–2.8)
  - PE (RR 0.81; 95% CI, 0.29–2.3)

LIMITATIONS:

- 5 of the 13 studies had a high risk of bias.
- VTE was a rare effect, leading to wide confidence intervals.
- There was heterogeneity in outcome definitions across studies; for example, one study measured VTE as DVT, another study defined VTE as DVT and PE, etc.
- Unclear if included studies used pre-specified criteria to define a VTE event.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

Does an Educational Video on Pain Management Decrease Opioid Use After a Cesarean Delivery?

Educational Video on Pain Management and Subsequent Opioid Use After Cesarean Delivery: A Randomized Controlled Trial

Mokhtari NB, Saeed H, Kawakita T, Huang JC, Iqbal SN. Educational Video on Pain Management and Subsequent Opioid Use After Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol.* 2021;138(2):253-259. doi:10.1097/AOG.0000000000004468

KEY TAKEAWAY: An educational video on pain management significantly decreased opioid use in women who delivered via cesarean section from the day of discharge through 14 days postpartum.

STUDY DESIGN: Randomized, non-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pain management after a cesarean delivery typically involves a multimodal regimen that includes opioid medication. Leftover opioid medication or prescribing too many at discharge can lead to an increased risk for accidents or chronic opioid use. There is a lack of research on the influence of patient education on pain management and opioid use. This study aims to evaluate whether viewing an educational video on pain management reduces opioid use after cesarean delivery.

PATIENTS: Adult women who delivered via cesarean section

INTERVENTION: Educational video on pain management + usual pain management instructions

CONTROL: Usual pain management instructions

PRIMARY OUTCOME: Number of oxycodone tablets used after discharge through postpartum day 14

Secondary Outcome: Adjuvant medication use, pain, satisfaction with pain control

METHODS (BRIEF DESCRIPTION):

- Women at least 18 years old who delivered via cesarean delivery at a tertiary medical center were eligible for the study.
- Women were excluded if they had a contraindication to NSAIDs or acetaminophen use, experienced a complicated cesarean delivery (hysterectomy, bowel/bladder injury, or need for reoperation), had a history of opioid use disorder or were non-English speaking.
- Eligible women were approached at discharge. After consent, randomization occurred, and women were enrolled to either view a five-minute educational video on pain management in addition to usual discharge pain medication instructions or to receive usual discharge pain medication instructions.
    - To ensure patients viewed the content, research staff were present for the duration of the video for availability and to ensure no problems occurred.
- Both groups completed a survey before discharge of basic demographics, pain scores, and breastfeeding/bottle feeding.
- Women in both groups received oxycodone 5 mg tablets (1 tablet every 4–6 hours as needed, dispensed 20 tablets) and ibuprofen 600 mg (take 1 tablet every 4–6 hours as needed, dispensed 40 tablets).
- All participants received a telephone call on postpartum day seven and day 14 after their cesarean delivery to complete a second survey and to quantify the remaining oxycodone and ibuprofen tablets.
- Participants also sent a picture to verify their report, rated their current pain (0–10), and rated their satisfaction with pain control on a five-point Likert scale (very satisfied, somewhat satisfied, neutral, somewhat dissatisfied, or very dissatisfied).
- All analysis was performed using the intention to treat principle.
- Analyses were performed using the Fisher exact test, two-sample t-test, or Wilcoxon rank-sum testing. All statistics were performed using SAS 9.4.

INTERVENTION (# IN THE GROUP): 24

COMPARISON (# IN THE GROUP): 24

FOLLOW-UP PERIOD: 14 days postpartum

RESULTS:

Primary Outcome –

- Participants who viewed the educational video utilized fewer oxycodone tablets compared to the control group from the day of discharge through:
    - Postpartum day 14 (median 1.5, range 0–20 vs median 10, range 0–24, respectively; *P*<.001)

    - Postpartum day seven (median 1.0, range 0–14 vs median 7.0, range 0–17, respectively; *P*<.001)

Secondary Outcome –

- There was no statistically significant difference between adjunct medication use, pain, and satisfaction with pain control between groups.

LIMITATIONS:

- The Hawthorne effect was assumed to be present because the number of oxycodone tablets used by participants in both groups was less than anticipated.
- The patient population was homogenous with the majority being Black.
- The educational video was in English, thus limiting the recruitment of non-native English speakers.
- There was no follow-up regarding how the participants disposed of their unused oxycodone tablets even though safe disposal was mentioned in the educational video.

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Risk Stratification Model for Preterm Birth in Preeclampsia

PREPARE: A Stepped-Wedge Cluster-Randomized Trial to Evaluate Whether Risk Stratification Can Reduce Preterm Deliveries Among Patients with Suspected or Confirmed Preterm Preeclampsia

De Oliveira L, Roberts JM, Jeyabalan A, et al. PREPARE: A Stepped-Wedge Cluster-Randomized Trial to Evaluate Whether Risk Stratification Can Reduce Preterm Deliveries Among Patients With Suspected or Confirmed Preterm Preeclampsia. *Hypertension*. 2023;80(10):2017-2028. doi:10.1161/HYPERTENSIONAHA.122.20361

KEY TAKEAWAY: The risk stratification model did not reduce preterm births, but the biomarker soluble fms-like tyrosine kinase/placental growth factor (sFlt-1/PlGF) ratio may be useful in predicting the development of severe features in preeclamptic patients.

STUDY DESIGN: Cluster randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Early delivery in patients with preterm preeclampsia is often necessary to reduce maternal morbidity and mortality but comes with significant risks to the neonate. Effective identification of patients at risk for developing preeclampsia with severe features may help anticipate the need for escalation of interventions in high-risk patients and help reduce unnecessary interventions in low-risk patients.

PATIENTS: Patients with preeclampsia

INTERVENTION: Clinical and laboratory risk assessment model

CONTROL: Routine care without risk assessment

PRIMARY OUTCOME: Preterm deliveries

METHODS (BRIEF DESCRIPTION):

- Patients with confirmed or suspected preeclampsia between 20+0 weeks and 36+6 weeks gestation were included and randomly assigned in clusters to the intervention group vs routine care.
    - Multifetal gestations, those with a diagnosis of fetal demise, and those who presented with conditions necessitating immediate delivery upon admission were excluded.
- The intervention group was risk-stratified based on the full preeclampsia integrated estimate of risk (fullPIERS) model, in addition to the sFlt-1/PlGF biomarker ratio.
    - FullPIERS is a risk calculator that yields the percent probability of adverse maternal outcomes within 48 hours.
- For patients in the intervention group who were deemed low-risk (fullPIERS <10% and sFlt-1/PlGF ≤ 38), clinicians were advised to defer delivery and continue routine care.
- For those who were not low-risk (fullPIERS >10% and sFlt-1/PlGF >38), clinicians were advised to increase surveillance.
- The proportion of preterm deliveries to total deliveries of this intervention group was compared to that of the control group which was not risk-stratified.

INTERVENTION (# IN THE GROUP): 586

COMPARISON (# IN THE GROUP): 563

FOLLOW-UP PERIOD: Up to 40 weeks

RESULTS:

Primary Outcome –

- The risk stratification model did not significantly reduce preterm deliveries in patients with preterm preeclampsia (adjusted odds ratio 0.79; 95% CI, 0.51–1.2).
- An sFlt-1/PlGF ratio ≤38 had a negative predictive value of 99% for identifying patients without severe features (no preeclampsia, eclampsia, or HELLP syndrome).
- An sFlt-1/PlGF ratio >38 had a sensitivity of 88% and specificity of 80% in identifying patients who would go on to develop preeclampsia with severe features, eclampsia, and HELLP syndrome.

LIMITATIONS:

- The sampling pool was limited to patients at community hospitals serving low-income areas of Brazil.
- Participating clinicians had an increased knowledge base and experience with the identification and treatment of preeclampsia, which may have impacted outcomes.

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Not All Creatine Is Created Equal: Different Outcomes in Use of Commonly Available Creatine Supplements

Creatine Monohydrate Supplementation, But Not Creatyl-L-Leucine, Increased Muscle Creatine Content in Healthy Young Adults: A Double-Blind Randomized Controlled Trial

Askow AT, Paulussen KJM, McKenna CF, et al. Creatine Monohydrate Supplementation, but not Creatyl-L-Leucine, Increased Muscle Creatine Content in Healthy Young Adults: A Double-Blind Randomized Controlled Trial. *Int J Sport Nutr Exerc Metab*. 2022;32(6):446-452. Published 2022 Aug 25. doi:10.1123/ijsnem.2022-0074

KEY TAKEAWAY: Supplementation with creatine monohydrate increases muscle concentration of creatine at two weeks compared to baseline, the creatyl-L-leucine group, and the placebo group.

STUDY DESIGN: Single-site, randomized, placebo-controlled, double-blind trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Creatine is a long-studied tripeptide dietary supplement with evidence as an ergogenic for strength and lean body mass when paired with resistance training. Creatine is a naturally occurring supplement when in higher concentrations benefits by increased muscle fiber workload, improved cell signaling, increase in anabolic hormones, improved cell hydration, and reduction in protein breakdown, collectively allowing improvement in athletic performance. Various analogs and blends of creatine have been incorporated into consumer supplements claiming to increase bioavailability, efficacy, and safety.

PATIENTS: Healthy adults 18–50 years old

INTERVENTION: Creatine monohydrate (CrM) or creatyl-L-leucine (CLL)

CONTROL: Placebo

PRIMARY OUTCOME: Muscle creatine concentration Secondary Outcome: Fasting plasma glucose, blood pressure, body mass, BMI, daily energy expenditures from physical activity within any groups

METHODS (BRIEF DESCRIPTION):

- 29 participants who were male (17) or female (12) with a BMI of 18–29 kg/m2 were included in the study.
- Exclusion criteria included allergies or hypersensitivity to anesthetics, notable metabolic cardiovascular, hepatorenal, autoimmune, or neuromuscular conditions, tobacco use, bleeding dyscrasias, prior ergogenic supplementation 12 months prior, or increased protein intake (>1.2 g/kg/day).
- Subjects had to follow a standard US diet and could not consume more than 100–200 mg of caffeine per day.
- Participants were randomized to receive daily 5 mg doses of CrM, CLL, or placebo.
- Participants completed three-day diet records to characterize dietary habits, macronutrient needs, and energy consumption to better quantify differences among groups.
- Muscular strength was assessed by testing 10-repetition max with leg extension, chest press, leg press, shoulder press, leg curl, and seated rows.
- Baseline muscle biopsy was obtained to determine creatine levels.
- Within each test group, participants participated in three supervised resistance training sessions per week for two weeks. The overall activity was monitored with accelerometers.
- Lean body mass was quantified via DEXA scan.
- Participants' sleep and periods of not wearing a monitoring device were recorded.
- A secondary four-day diet record was obtained again to quantify any differences in energy intake vs expenditure during the 14-day trial.
- The second comparative DEXA scan and muscle biopsy were obtained after the supplementation period concluded.

INTERVENTION (# IN THE GROUP):

- Creatine monohydrate: 8
- Creatyl-L-Leucine: 11

COMPARISON (# IN THE GROUP): 10

FOLLOW-UP PERIOD: Two weeks

RESULTS:

Primary Outcome –

- CrM supplementation improved muscle creatine content at two weeks compared to baseline (43 vs 53 mmol/kg wet weight [WW]; *p*=.01).

- CLL supplementation did not improve muscle creatine content at two weeks compared to baseline (39 vs 40 mmol/kg WW; *p*=.680).

Secondary Outcome –

- There were no significant differences in fasting plasma glucose, systolic blood pressure, body mass, BMI, or daily energy expenditures from physical activity within any groups.

LIMITATIONS:

- This was a single-center study with a small study size.
- Exclusion criteria notably reduced the test population.
- Adolescent and teen athlete populations were excluded.
- No creatine "loading phase" is included to optimally test creatine absorption and final muscle concentration.

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