GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Does Aspirin Increase GI Bleeding Risk in Older People?

Does Aspirin Increase GI Bleeding Risk in Older People?

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SPOTLIGHT

Major GI Bleeding in Older Persons Using Aspirin: Incidence and Risk Factors in the ASPREE Randomised Controlled Trial

Mahady SE, Margolis KL, Chan A, et al. Major GI bleeding in older persons using aspirin: incidence and risk factors in the ASPREE randomised controlled trial. *Gut*. 2021; 70(4):717–724. doi:10.1136/gutjnl-2020-321585

KEY TAKEAWAY: Aspirin may increase GI bleeding risk in older people. This risk is more pronounced in those who smoke, have hypertension or CKD, are older, or are obese.

STUDY DESIGN: Multisite, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Aspirin is a commonly prescribed medication that is typically prescribed to prevent vascular events; however, this can come at a cost of GI bleeds. The ASPREE trial aims to narrow the research gap regarding the incidence of GI bleeding due to aspirin.

PATIENTS: Older people without high risk of bleeding

INTERVENTION: Daily enteric-coated aspirin

CONTROL: Placebo

OUTCOME: Major GI bleeding that required transfusion, hospitalization, surgery, or death

METHODS (BRIEF DESCRIPTION):

- 19,114 participants were included with 9,525 assigned to aspirin and 9,589 assigned to placebo.
- Inclusion criteria: ≥70 years old (≥65 in US minority groups) without CV disease, dementia, significant physical disability, or any illness expected to limit life expectancy to five years or less
- Exclusion criteria: high risk of bleeding, anemia, use of aspirin for secondary prevention, or contraindication to aspirin, concurrent use of anticoagulants or antiplatelet agents
- Participants were randomized to aspirin or placebo group and given a one-year supply of medication at a time.
- Participants, medical practitioners, and study staff were blinded.
- Median follow-up time was 4.7 years.
- Patients were followed-up every 3-months via telephone interviews with yearly in-person interviews.
- Primary outcome of major GI bleeding event had to meet the following criteria: 1) substantiated by medical documentation 2) bleeding that required hospitalization, transfusion, surgery, or death

INTERVENTION (# IN THE GROUP): 9,525
COMPARISON (# IN THE GROUP): 9,589

FOLLOW UP PERIOD: Median of 4.7 years

RESULTS:

- Aspirin increased the risk of upper GI bleeding events compared to placebo (89 vs 48; *P*<.01)
- Aspirin did not increase the risk of lower GI bleeding events compared to placebo (73 vs 54; *P*=.08).
- Overall, the aspirin group had a 60% increase in GI bleeding.
  - Risk factors that contributed to an increased risk of GI bleeding included increased age, smoking, hypertension, CKD, and obesity.
- Aspirin increased the absolute five-year risk of GI bleeding for people taking aspirin with the additional risk factors mentioned above (smoking, hypertension, etc.).
  - The risk increased to 2.3% for people 70 years old (95% CI, 1.1%–4.0%).
  - The risk increased to 5.0% for people 80 years old (95% CI, 2.6%–8.7%).

LIMITATIONS:

- People with previous major bleeding episodes or conditions with high bleeding risk were excluded.
- Patients were not tested for *H. pylori*.
- Bleeding events that did not require transfusion, hospitalization, surgery, or death were not included.
- Absolute five-year risk had wide CI, especially as more risk factors were present, indicating insufficient power despite a large sample size. This could be due to the heterogeneity of the population caused by accounting for the variability of risk factors.

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6 Hours of Cervical Ripening by Double-Balloon Decreases Induction Time and Maternal-Fetal Infection Risk

Double-Balloon Device for 6 Compared With 12 Hours for Cervical Ripening

Bleicher I, Dikopoltsev E, Kadour-Ferro E, et al. Double-Balloon Device for 6 Compared With 12 Hours for Cervical Ripening: A Randomized Controlled Trial. *Obstet Gynecol*. 2020; 135(5):1153–1160. doi:10.1097/AOG.0000000000003804

KEY TAKEAWAY: Six hours of double-balloon insertion decreases time to delivery and risk of intrapartum fever for both nulliparous and parous women compared to 12 hours.
STUDY DESIGN: Prospective, randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Approximately a quarter of all deliveries in first world countries involve the induction of labor. One of the two most common methods of cervical ripening to promote favorability and shorten labor induction time is via mechanical intervention, including balloon catheter placement. This is the first randomized controlled trial to examine the risks and benefits of duration of use of double-balloon catheters.

PATIENTS: Adult nulliparous and parous women
INTERVENTION: Six hours of double-balloon catheter placement
CONTROL: 12 hours of double-balloon catheter placement
OUTCOME: Time to delivery, cervix favorability, indication for cesarean delivery, intrapartum fever

METHODS (BRIEF DESCRIPTION):

- Patients were nulliparous and multiparous women admitted for induction of labor.
  - Inclusion Criteria: With term pregnancies and Bishop scores <5, singleton pregnancy, cephalic presentation
  - Exclusion Criteria: History of cesareans, ruptured membranes, laboring patients, or other contraindications for vaginal delivery
- Patients were randomized into either double-balloon placement for six or 12 hrs.
- Balloon placement was standardized to be performed by an on-call physician every evening, regardless of when the patients were admitted that day, and was placed via manufacturer's instructions, using 40 mL of normal saline in both internal and external balloons.
- After device removal, either at the designated time or following spontaneous expulsion, a second Bishop score was collected.
- If cervix was favorable AROM was performed, and oxytocin initiated. If cervix remained unfavorable, Cytotec was given.
- The primary outcome was identifying time to delivery after the catheter insertion.
- This study used Student's T-test, Mann-Whitney U test and Fisher exact tests, as appropriate. A two-way ANOVA with interaction term was used to compare nulliparous and parous groups.

INTERVENTION (# IN THE GROUP):
Multiparous six hour group: 49
Nulliparous six hour group: 48
COMPARISON (# IN THE GROUP):
Multiparous 12 hour group: 47
Nulliparous 12 hour group: 53

FOLLOW UP PERIOD: From double-balloon insertion to delivery

RESULTS:

- Six hours of cervical ripening decreased time to delivery compared to 12 hours in nulliparous women (mean difference [MD] 5.8 hrs; 95% CI, 0.2–11).
- Six hours of cervical ripening decreased time to delivery compared to 12 hours in parous women (MD 4.7 hrs; 95% CI, 1.6–7.8).
- There was no difference in cervix favorability or indication for cesarean delivery between groups.
- Six hours of cervical ripening decreased the risk of intrapartum fever by 8% compared to the 12 hours group (OR 5.3; 95% CI, 1.1–25).

LIMITATIONS:

- Results cannot be extrapolated to outcomes using a single-balloon catheter.
- Participants and study personnel were not blinded to ripening time.
- Significant differences in cesarean delivery rate and women's satisfaction were not shown.
- Study could not demonstrate a shorter time to delivery from admission due to standardized time of double-balloon insertion.
- The study was potentially underpowered due to a small sample size when looking at data related to intrapartum fever.

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Aerobic Exercise Reduces Concussion Symptoms and Recovery Time

Therapeutic Effect of Aerobic Exercise for Adolescents After Mild Traumatic Brain Injury and Sport-Related Concussion: A Meta-Analysis from Randomized Controlled Trials

Shen X, Gao B, Wang Z, et al. Therapeutic Effect of Aerobic Exercise for Adolescents After Mild Traumatic Brain Injury and Sport-Related Concussion: A Meta-Analysis from Randomized Controlled Trials. *World Neurosurg*. 2021; 146:e22-e29. doi:10.1016/j.wneu.2020.09.143

KEY TAKEAWAY: In patients with mild traumatic brain injury and sport-related concussion, aerobic exercise may shorten the time to recovery and reduce symptoms but does not affect neurocognitive function.

STUDY DESIGN: Meta-analysis of 5 RCTs (N=203)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Treatment for mild traumatic brain injury (mTBI), including sport-related concussion (SRC), has traditionally focused on slow reintroduction of activity. However, recent studies have shown conflicting data on the benefits of exercise during the recovery period.

PATIENTS: Patients 12-19 years old with mTBI

INTERVENTION: Aerobic exercise

CONTROL: Traditional symptom-based reintroduction of activity

OUTCOME: Symptom severity, time to recovery, neurocognitive function

Secondary Outcomes: Determine if the type of mTBI (SRC or not) effected treatment outcome; determine if the time to initial assessment (<3 weeks or ≥3 weeks) effected treatment outcome

METHODS (BRIEF DESCRIPTION):

- Adolescents between 12 and 19 years old with mTBI (including SRC) were included in the study.
- Symptom severity was based on Post Concussion Symptom Scale (PCSS). PCSS scores range from 0 (no symptoms) to 132 (maximum symptoms in 22 categories).
- Neurocognitive function was assessed by Immediate Post-concussion Assessment and Cognitive Testing (ImPACT). ImPACT normative scores differ by age and gender; lower score means lower performance on measurements such as memory, motor speed, and reaction speed.
- Differing treatment protocol per study, but all used some version of submaximal, progressive sub-symptomatic aerobic exercise, including bicycle and treadmill.
- Time to recovery was not defined in this meta-analysis. The three RCTs which were analyzed for time to recovery defined it as either symptom-free after physical exertion, or symptom normalization with exhaustive exercise.
- Changes reported as mean difference (MD, or weight mean difference, WMD) for PCSS and ImPACT.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Not available

RESULTS:

Primary Outcomes –

- Aerobic exercise improved mTBI symptoms more than traditional symptom-based activity reintroduction (4 trials, N=202; weighted mean difference [WMD] -4.8; 95% CI, -8.8 to -0.8; I^2=27%).
- Aerobic exercise improved day to recovery more than traditional symptom-based activity reintroduction (3 trials, N=185; mean difference [MD] -3.9 days; 95% CI, -6.5 to -1.2; I^2<0.01).
- There was no significant change to neurocognitive function between aerobic exercise and traditional symptom-based activity reintroduction (2 trials, N=47).

Secondary Outcomes –

- Subgroup analysis found that the type of mTBI (SRC or not) and the time to presentation (<3 weeks or ≥3 weeks) had no statistically significant effects on treatment outcomes.

LIMITATIONS:

- Patients and research assistants were unblinded to intervention/control status.
- Primary outcomes reflect overlapping but not identical populations:
  - Two studies assessed ImPACT (only 47 subjects, limiting confidence).
  - Four studies assessed PCSS.
  - Three studies assessed days to recovery.
- Many patients withdrew from studies as the intervention progressed.
- Follow-up periods were not defined.

- Unclear funding source(s).

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Getting Hip: Treatment for Greater Trochanteric Pain Syndrome

Comparative Efficacy of Nonoperative Treatments for Greater Trochanteric Pain Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Gazendam A, Ekhtiari S, Axelrod D, et al. Comparative Efficacy of Nonoperative Treatments for Greater Trochanteric Pain Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials [published online ahead of print, 2021 Mar 12]. *Clin J Sport Med.* 2021; 10.1097/JSM.0000000000000924. doi:10.1097/JSM.0000000000000924

KEY TAKEAWAY: For adult patients with Greater Trochanteric Pain Syndrome (GTPS), Platelet Rich Plasma (PRP) injection and shockwave therapy significantly improve pain at one to three months. Structured exercise also results in significantly improved functional outcomes at one to three months.

STUDY DESIGN: Systematic review and network meta-analysis of 13 randomized controlled trials (N=1,034)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Proposed pathophysiology and definition of GTPS has expanded in recent years. New treatment modalities have been utilized given the changes in understanding of lateral hip pain. Previous review articles on this subject have included non-randomized study designs and have not studied more than two treatment modalities at a time. This study represents the first systematic review and meta-analysis using only RCT's to compare the efficacy of various nonoperative treatment modalities for pain and functional status in adults with GTPS.

PATIENTS: Adults with Greater Trochanteric Pain Syndrome (GTPS)

INTERVENTION: Structured exercise, blinded corticosteroid injection, guided corticosteroid injection, platelet-rich plasma injection, shockwave therapy, hyaluronic acid injection, and dry needling

CONTROL: No treatment or treatments compared to one another

OUTCOME: Pain

Secondary Outcome: Function

METHODS (BRIEF DESCRIPTION):

- A literature search for GTPS performed on PubMed, Embase, Cochrane, ScOPUS, and Web of Science for nonoperative treatments of GTPS was conducted and only included RCTs measuring pain or function when comparing nonoperative GTPS treatments in adult patients.
- All pain and functional status outcome scores were converted to the Visual Analogue Scale (pain scored from 0-10, higher scores=more pain) or the Harris Hip Score (functional outcome scored 0-100, higher scores=better function).
- Heterogeneity, inconsistency, and transitivity analyses across treatment comparisons were conducted.

INTERVENTION (# IN THE GROUP):

- Blinded corticosteroid injection: 267
- Guided corticosteroid injection: 125
- Structured exercise: 191
- Shockwave therapy: 104
- Platelet-rich plasma injection: 76
- Hyaluronic acid injection: 25
- Dry needling: 21
- Placebo intervention: 96

COMPARISON (# IN THE GROUP):

- No treatment: 129

FOLLOW UP PERIOD: One to three months and six to 12 months

RESULTS:

Primary Outcome –

- PRP injection resulted in a statistically significant pain reduction at one to three months compared to no treatment (MD -3.6; 95% CI, -6.6 to -0.34).
- Shockwave therapy resulted in a statistically significant pain reduction at one to three months compared to no treatment (MD -3.2; 95% CI, -6.1 to -0.22).
- Blinded corticosteroid injection, dry needling, guided corticosteroid injection, hyaluronic acid, placebo intervention, and structured exercise did not result in a statistically significant pain reduction at one to three months or six to 12 months compared to no treatment.

Secondary Outcome –

- Structured exercise resulted in a statistically significant improvement in functional outcome scores at one to three months compared to no treatment (MD 24; 95% CI, 1.7–46).
- Blinded corticosteroid injection, dry needling, guided corticosteroid injection, placebo intervention, platelet-rich plasma injection, and shockwave therapy did not

result in statistically significant improvement in functional outcome scores at one to three months compared to no treatment.

LIMITATIONS:

- Most studies only included short follow-up periods.
- Placebo interventions varied among groups.
- Most trials consisted of small sample sizes with poor statistical power.
- Heterogeneity between studies is likely present because of differences in diagnosis and diagnostic criteria of GTPS over the ten-year period of the study.

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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 Army Medical Department, the Army at large, or the Department of Defense.