GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 5 - Issue 9

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 3-7, 2025

SPOTLIGHT:

Choosing Intra-Articular Injections for Knee Osteoarthritis

Choosing Intra-Articular Injections for Knee Osteoarthritis

Intra-Articular Platelet-Rich Plasma Injections vs Intra-Articular Corticosteroid Injections for Symptomatic Management of Knee Osteoarthritis: Systematic Review and Meta-Analysis

McLarnon M, Heron N. Intra-articular platelet-rich plasma injections versus intra-articular corticosteroid injections for symptomatic management of knee osteoarthritis: systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2021;22(1):550. Published 2021 Jun 16. doi:10.1186/s12891-021-04308-3

KEY TAKEAWAY: Platelet-rich plasma (PRP) injections improve pain at six months compared to corticosteroid (CS) injections. However, intra-articular (IA) PRP does not have a significant impact on return to sports or activity participation at six months.

STUDY DESIGN: Meta-analysis and systemic review of eight studies of various designs (N=648)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: IA CS injections are one of the most common treatment modalities for symptomatic knee osteoarthritis (OA). IA PRP injections have proven to be a promising alternative. However, there are no previous systematic reviews comparing outcomes between IA PRP and CS injections. This study aimed to investigate the potential for improved outcomes using IA PRP injections compared to CS injections for the symptomatic management of knee OA.

PATIENTS: Adults with symptomatic knee OA

INTERVENTION: IA PRP injections

CONTROL: IA CS injections

PRIMARY OUTCOME: Pain and sports or activity participation

Secondary Outcome: Pain at one, three, nine, and 12 months

METHODS (BRIEF DESCRIPTION):

- The study is reported per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.
- Eight published trials comparing IA PRP and CS injections for knee OA were included and published between 2017 and 2019.
- Studies that compared IA PRP injections to IA CS injections in patients ≥18 years old with symptomatic knee OA were included in the study.
- For adolescents <18 years old, studies using co-interventions alongside either PRP or CS injections and studies not comparing IA PRP directly to IA CS injections were excluded from the review.
- The dosing/concentration and frequency range of PRP or CS injections were not stated in this meta-analysis.
  - Route: Intra-articular
  - Duration: 3–12 month intervals
- Pain was assessed as one of the primary outcomes using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the visual analog scales (VAS) at six months post-intervention
  - Higher scores on the WOMAC index represent worse function, pain, and stiffness.
  - A higher score on the VAS represents a higher level of pain.
- Sports or activity participation was assessed as the other primary outcome using the Knee Injury and Osteoarthritis Outcome Score (KOOS) assessment at six months.
  - Lower scores on the KOOS represent worse knee function and ability.
- The secondary outcome measured the pain score reduction at one, three, nine, and 12 months post-intervention using the WOMAC index and VAS.

INTERVENTION (# IN THE GROUP): 295

COMPARISON (# IN THE GROUP): 275

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- IA PRP injections significantly reduced pain compared to IA CS injections at six months (7 studies, n=545; pooled standardized mean difference [SMD] –0.78; 95% CI, –1.3 to –0.23; I^2=88%).
- IA PRP injections did not significantly affect sports or activity participation compared to IA CS injections at six months (2 studies, n=132; mean difference [MD] 9.7; 95% CI, –0.45 to 20; I^2=69%).

Secondary Outcome –

- IA PRP injections did not significantly reduce pain compared to IA CS injections at one month and 12 months
- IA PRP injections reduced pain compared to IA CS injections at three months (6 studies, n=424; pooled SMD –0.51; 95% CI, –0.90 to –0.12; I^2=72%).
- IA PRP injections reduced pain compared to IA CS injections at nine months (1 study, n=80; pooled SMD –1.6; 95% CI, –2.1 to –1.1; I^2=N/A).

LIMITATIONS:

- Significant diversity between study injection protocols and length of follow-up.
- Large diversity in patient age and gender between studies, with females making up 68% of participants.
- Variable preparation methods of PRP, resulting in differing concentrations and yields between the studies complicate therapeutic analysis.

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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 US Government.

Mepivacaine Instillitation for Pain Reduction During Intrauterine Device Placement in Nulliparous Women: A Double-Blinded Randomized Trial

Envall N, Elgemark K, Kopp Kallner H. Mepivacaine instillation for pain reduction during intrauterine device placement in nulliparous women: a double-blinded randomized trial. *Am J Obstet Gynecol*. 2024;231(5):524.e1-524.e7. doi:10.1016/j.ajog.2024.05.038

KEY TAKEAWAY: The instillation of mepivacaine significantly reduces pain during intrauterine device (IUD) placement and increases the tolerability of pain during placement compared to placebo.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: IUDs are among the most effective reversible contraception methods available. However, fear of pain associated with placement is a barrier to patients selecting this method. At present, there is no highly accepted pharmacological intervention for effective pain reduction during IUD placement.

PATIENTS: Nulliparous women seeking IUD placement

INTERVENTION: Intrauterine mepivacaine

CONTROL: Placebo

PRIMARY OUTCOME: Pain during IUD placement

Secondary Outcome: Pain at installation and 10 minutes after placement, tolerability of pain

METHODS (BRIEF DESCRIPTION):

- The study included nulliparous women 18–31 years old who opted for a 52 mg levonorgestrel hormone IUD (Mirena) for contraception.
- Inclusion criteria included the ability to comprehend oral and written information in either Swedish or English, willingness to undergo randomization, complete study questionnaires, and confirmed negative pregnancy test.
- Exclusion criteria included the current use of an IUD, a known uterine or cervical abnormality, an increase in bleeding risk, or the use of any other method for pain relief prior to placement (oral analgesics).
- The study was conducted in 12 centers strategically located in both rural and urban areas.
- Providers included midwives and gynecologists experienced with IUD placement.
- Randomized patients received either intrauterine mepivacaine (10 mL of 20 mg/mL) or intrauterine sodium chloride (10 mL of 9 mg/mL).
- Participants assessed their current pain level and worst menstrual cramping during typical menstruation on a 100 mm visual analog scale (VAS), with zero indicating “no pain” and 100 mm indicating “worst pain imaginable.”
- The patient’s pain levels were evaluated at baseline (prior to examination) and momentarily after intrauterine instillation, IUD placement, and at 10 minutes following speculum removal.
- Patients were asked to rate the tolerability of the pain and their overall satisfaction with the procedure.

INTERVENTION (# IN THE GROUP): 76

COMPARISON (# IN THE GROUP): 75

FOLLOW-UP PERIOD: 10 minutes

RESULTS:

Primary Outcome –

- The intrauterine instillation of mepivacaine reduced pain during IUD placement (13 mm; 95% CI, 5.8–21).

Secondary Outcome –

- There was no significant difference in pain scores at IUD instillation for intrauterine mepivacaine compared to placebo.
- There was no significant difference in pain scores at 10 minutes after IUD placement for intrauterine mepivacaine compared to placebo.
- Participants in the mepivacaine group reported higher pain tolerability during IUD placement compared to placebo (93% vs 80%, respectively; *p*=.02)

LIMITATIONS:

- Certain factors that could influence pain during the placement procedure (anticipated pain, anxiety, etc.) were not systematically assessed.
- The evaluation focused exclusively on one type of IUD (Mirena), which may limit the generalizability of the findings to different IUD types.

- Only experienced providers participated in the study, which may limit generalizability to settings with less experienced providers.

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Does Playing Surface Really Play a Major Part in Sports-Related Concussion Symptoms?

Impact of Playing Surface on Concussion Symptoms in Young American Football Players

Heinzelmann MM, Stokes M, Miller SM, et al. Impact of Playing Surface on Concussion Symptoms in Young American Football Players. *Clin J Sport Med*. 2024;34(4):357-361.
doi:10.1097/JSM.0000000000001204

KEY TAKEAWAY: Grass playing surfaces may cause more significant concussion symptoms with helmet-to-ground impact than artificial turf playing surfaces.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Since artificial turf was introduced in the 1960s, there has been conflicting evidence and opinion on whether natural grass or artificial turf is safer to play on. Up to 30% of sports-related concussions (SRC) in American football occur from helmet-to-ground contact. Little research has been done to show if playing surface plays a role in SRC.

PATIENTS: Male American football players 10–24 years old with a helmet-to-ground concussion

INTERVENTION: Artificial playing surface

CONTROL: Natural grass playing surface

PRIMARY OUTCOME: Concussion severity symptoms

Secondary Outcome: Individual concussion symptoms

METHODS (BRIEF DESCRIPTION):

- Adolescents and adult male American Football players who were registered in the North Texas Concussion Registry and who sustained a helmet-to-ground concussion that presented to a specialty concussion clinic within 14 days of sustaining the injury were included in the study.
- The patient's demographics, time since injury, history of headache, history of concussion(s), playing surface, and post-concussive symptoms were collected using a self-report questionnaire.
- The Sports Concussion Assessment Tool 5th edition (SCAT5) was used to collect concussive symptoms and severity.
    - The SCAT5 is a standardized tool for evaluating a suspected concussion that is specifically designed for use by medical professionals.
    - The SCAT5 scoring summary includes the following sections:
        - Red flags, memory assessment, Glasgow Coma Scale, cervical spine assessment, symptom evaluation, cognitive screening, neurological screening, balance examination, and delayed recall
    - Scores of the SCAT5 range from 0–132, with higher scores indicating worse symptom severity.
- The natural grass and turf groups were similar in all aspects of the self-reported questionnaire except age.
    - Patients in the artificial turf group (mean 15 years old) were older than those in the natural grass group (mean 14 years old).
- Statistical analysis was done with the Chi-square test (for a history of concussion), Fischer exact test (history of headache and absence/presence of symptoms), and Fisher-Freeman-Halton exact test (for the number of previous concussions).
    - Continuous variables were analyzed with independent samples t-tests.

INTERVENTION (# IN THE GROUP): 29

COMPARISON (# IN THE GROUP): 33

FOLLOW-UP PERIOD: Single assessment within 14 days of concussion

RESULTS:

Primary Outcome –

- Participants with an SRC on natural grass reported worse symptom severity compared to participants on artificial turf (27 vs 12; *P*=.005).
- Participants with an SRC on natural grass reported a higher total number of symptoms compared to participants on artificial turf (10 vs 5.9; *P*=.006)

Secondary Outcome –

- Participants with an SRC on natural grass had a higher likelihood of developing individual concussion-related symptoms compared to artificial turf:
    - Dizziness (52% vs 10%; *P*<.001)
    - Blurred vision (46% vs 3.4%; *P*<.001)
    - Sensitivity to noise (51% vs 24%; *P*=.027)
    - Feeling "in a fog" (49% vs 17%; *P*=.009)

- Difficulty remembering (61% vs 24%; *P*=.004)
- Fatigue or low energy (67% vs 38%; *P*=.024)
- Confusion (33% vs 10%; *P*=.031)

LIMITATIONS:

- Small sample size
- The geographic location was limited to Texas.
- Athletes were older in the artificial playing surface group.
- The study included only male participants.
- Condition of grass or turf
- Unknown if SRC occurred during the game or practice
- Only a single post-injury assessment was conducted on the included athletes.

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D-Dimer as a Diagnostic Tool for Acute Aortic Syndromes

Diagnostic Accuracy of D-Dimer for Acute Aortic Syndromes: Systematic Review and Meta-Analysis

Essat M, Goodacre S, Pandor A, Ren S, Ren S, Clowes M. Diagnostic Accuracy of D-Dimer for Acute Aortic Syndromes: Systematic Review and Meta-Analysis. *Ann Emerg Med*. 2024;84(4):409-421. doi:10.1016/j.annemergmed.2024.05.001

KEY TAKEAWAY: D-dimer testing can help rule out acute aortic syndromes (AAS) in patients with a low clinical probability but carries the potential for false positives in low-risk populations.

STUDY DESIGN: Systematic review and meta-analysis of 25 cohort studies (n=9,228)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high heterogeneity among included studies)

BRIEF BACKGROUND INFORMATION: AAS encompasses life-threatening, urgent conditions affecting the thoracic aorta, including acute aortic dissection, intramural hematoma, and penetrating ulcer. D-dimer testing, which is more available than computed tomography (CT) angiography, may expedite the identification of identifying AAS. Uncertainty exists regarding which patients, based on pre-test probabilities, would most benefit from D-dimer testing in diagnosing AAS. This study investigated the diagnostic significance of D-dimer for addressing acute aortic syndrome.

PATIENTS: Patients presenting with suspected AAS

INTERVENTION: D-dimer testing

CONTROL: Reference standard testing

PRIMARY OUTCOME: Diagnostic accuracy

METHODS (BRIEF DESCRIPTION):

- The study included patients in Europe, Asia, and North America presenting to the emergency department with new onset back, chest, or abdominal pain, syncope, or symptoms caused by low perfusion.
- Patients with AAS following acute traumas or incidental findings were excluded.
- This systematic review excluded case-control studies, to reduce bias, leading to overestimation of diagnostic accuracy.
- The weighted prevalence of AAS across studies was 23%.
- D-dimer testing with and without a threshold of 500 ng/ml was compared to reference standards for diagnosing AAS (computed tomographic angiography [CTA], electrocardiogram [ECG] gated CTA, echocardiography, magnetic resonance angiography [MRA]) to calculate the sensitivity and specificity of D-dimer testing.

INTERVENTION (# IN THE GROUP): 7,978

COMPARISON (# IN THE GROUP): The same 7,978 patients

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- D-dimer testing had high sensitivity and moderate specificity for diagnosing AAS compared to standard testing.
  - Sensitivity (97%; 95% CI, 95–98)
  - Specificity (57%; 95% CI, 48–64)
  - Positive predictive value (2.2; 95% CI, 1.9–2.7)
  - Negative predictive value (0.06; 95% CI, 0.04–0.09)

LIMITATIONS:

- Some studies had potential bias due to unclear reporting and limited patient sampling strategies.
- There was high heterogeneity among the study designs in the selection of eligible patients and the definition of reference standards.
- This systematic review did not address the cost-effectiveness of D-dimer testing or its impact on patient management.

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Mapping the Loneliness Epidemic: A Global Perspective

The Prevalence of Loneliness Across 113 Countries: Systematic Review and Meta-Analysis

Surkalim DL, Luo M, Eres R, et al. The prevalence of loneliness across 113 countries: systematic review and meta-analysis. *BMJ*. 2022;376:e067068. Published 2022 Feb 9. doi:10.1136/bmj-2021-067068

KEY TAKEAWAY: Loneliness is a widespread global issue that affects various age groups with varying prevalence by region.

STUDY DESIGN: Systematic review and meta-analysis of 57 observational studies (N=not available)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to substantial variability among studies, methodologies, and measurement instruments)

BRIEF BACKGROUND INFORMATION: Loneliness is a common negative sensation that is an emerging public health concern due to its association with mental health disorders, cognitive decline, increased risks of cardiovascular disease (CVD), and reduced quality of life (QoL). The objective of the study was to examine the prevalence of loneliness globally across different age groups and to identify patterns, data gaps, and temporal trends of loneliness.

PATIENTS: Adolescents to older adults

INTERVENTION: No intervention

CONTROL: No control

PRIMARY OUTCOME: Prevalence of loneliness

Secondary Outcome: Temporal trends

METHODS (BRIEF DESCRIPTION):

- The meta-analysis was based on pre-COVID-19 pandemic data from 2000–2019 across 113 countries.
- The study examined loneliness across a wide age range, which included adolescents (10–17 years old), young adults (18–29 years old), middle-aged adults (30–59 years old), and older adults (≥60 years old).
- The study included observational research on loneliness prevalence with nationally representative samples and validated measures, excluding studies with small or non-representative samples (university students), unvalidated tools, or a focus on transient loneliness.
- The study analyzed both single-item and scale measures.
  - Single-item measures asked questions such as "How often do you feel lonely?" with varying response options, which had a moderate correlation with the standard scales, confirming their validity for assessing loneliness.
  - Scale measures included validated tools like the University of California, Los Angeles (UCLA) and de Jong Gierveld Loneliness Scales.
- Generalized linear mixed-effects models were applied to pool prevalence estimates, summarizing data regionally and by age group.
- Quality assessments were conducted using tools such as the Joanna Briggs Institute checklist to ensure methodological rigor.

INTERVENTION (# IN THE GROUP): Not applicable

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- The prevalence of loneliness among adolescents 12–17 years old in Africa was 13% (5 studies, 11 countries; 95% CI, 10–16).
- The prevalence of loneliness among adolescents 12–17 years old in the Americas was 12% (5 studies, 26 countries; 95% CI, 11–13).
- The prevalence of loneliness among adolescents 12–17 years old in the Western Pacific was 10% (4 studies, 12 countries; 95% CI, 7.7–13).
- The prevalence of loneliness among adolescents 10–17 years old in the Eastern Mediterranean was 14% (2 studies, 10 countries; 95% CI, 12–17).
- The prevalence of loneliness among adolescents 10–17 years old in Southeast Asia was 9.2% (5 studies, 9 countries; 95% CI, 6.8–12).
- The prevalence of loneliness among young adults 18–29 years old in Central &Western Asia was 4.1% (6 studies, 6 countries; 95% CI, 2.8–5.9).
- The prevalence of loneliness among young adults 18–29 years old in Eastern Europe was 7.5% (5 studies, 30 countries; 95% CI, 5.9–9.4).

- The prevalence of loneliness among young adults 18–29 years old in Northern Europe was 2.9% (5 studies, 30 countries; 95% CI, 1.8–4.5).
- The prevalence of loneliness among young adults 18–29 years old in Southern Europe was 5.4% (2 studies, 5 countries; 95% CI, 4.1–7.1).
- The prevalence of loneliness among young adults 18–29 years old in Western Europe was 4.9% (6 studies, 8 countries; 95% CI, 3.5–6.7).
- The prevalence of loneliness among middle-aged adults 30–59 years old in Central and Western Asia was 9.8% (6 studies, 6 countries; 95% CI, 5.1–18).
- The prevalence of loneliness among middle-aged adults 30–59 years old in Northern Europe was 2.7% (5 studies, 32 countries; 95% CI, 2.4–3.0).
- The prevalence of loneliness among middle-aged adults 30–59 years old in Southern Europe was 7.7% (2 studies, 5 countries; 95% CI, 6.1–9.6).
- The prevalence of loneliness among middle-aged adults 30–59 years old in Eastern Europe was 9.6% (5 studies, 32 countries; 95% CI, 7.7–12).
- The prevalence of loneliness among middle-aged adults 30–59 years old in Western Europe was 5.1% (5 studies, 9 countries; 95% CI, 4.0–6.5).
- The prevalence of loneliness among older adults ≥60 years old in Eastern Europe was 21% (17 studies, 38 countries; 95% CI, 19–24).
- The prevalence of loneliness among older adults ≥60 years old in Western Europe was 8.7% (17 studies, 38 countries; 95% CI, 7.3–11).
- The prevalence of loneliness among older adults ≥60 years old in Southern Europe was 16% (4 studies, 7 countries; 95% CI, 13–19).
- The prevalence of loneliness among older adults ≥60 years old in Northern Europe was 5.2% (5 studies, 5 countries; 95% CI, 4.2–6.5).

Secondary Outcome –

- The incidence of loneliness among early adolescents 11–15 years old in Danish school children increased from 4.4% in 1991 to 7.2% in 2014 (*P*<.001).
- The incidence of loneliness among Norwegian secondary school children increased from 9.0% in 2014 to 12% in 2018 (*P*<.001).
- The incidence of loneliness among adolescent school children in the Arab Emirates (2005–2016) and individuals ≥77 years old in Sweden (1992–2014) remained unchanged over the respective study periods.

LIMITATIONS:

- High degree of heterogeneity among study populations, methodologies, and measurement instruments
- Reporting bias was present from the use of subjective self-reported measures of loneliness.
- The perception and definition of loneliness may differ in different cultures and micro-cultures, even within the same country.

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