GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1 - Issue 4

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of January 25 - 29, 2021

SPOTLIGHT: OMT Shortens NICU Stay and Costs

OMT shortens NICU stay and costs in premature infants

Osteopathic Manipulative Treatment Showed Reduction of Length of Stay and Costs in Preterm Infants: A Systematic Review and Meta-Analysis.
Lanaro D, Ruffini N, Manzotti A, Lista G. Osteopathic manipulative treatment showed reduction of length of stay and costs in preterm infants: A systematic review and meta-analysis. *Medicine (Baltimore)*.2017; 96(12):e6408.

KEY TAKEAWAY: Osteopathic manipulative treatment (OMT) significantly decreases length of stay and cost of hospitalization in premature infants.
STUDY DESIGN: Meta-analysis of 4 RCTs and 1 nonrandomized observational study; N=1306
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Infant prematurity increases the risk of poor health outcomes, developmental and cognitive delays. The degree of prematurity directly effects development and hospitalization costs. The impact of OMT on preterm infants is uncertain. This systematic review evaluated the impact of OMT on length of stay and costs in preterm infants.
PATIENTS: Preterm infants clinically stable or recuperating from acute respiratory illness
INTERVENTION: OMT performed by osteopaths
CONTROL: Standard care or standard care plus sham OMT
OUTCOME: length of stay; cost reduction, weight gain, morbidity

METHODS (BRIEF DESCRIPTION): Authors performed comprehensive literature search from inception through May 2015 including grey literature and conference proceedings. Two authors independently selected and reviewed studies. Studies assessed for bias via Cochrane tools and heterogeneity via I2 statistic. Mean differences and relative risks calculated for outcomes. Intention-to-treat analysis conducted. Fixed effects method used for meta-analysis.

INTERVENTION (# IN THE GROUP): OMT (636) with gestational age between 23–38 weeks
COMPARISON (# IN THE GROUP): Standard Care with or without sham OMT (661) with gestational age between 24–36 4/7 weeks

FOLLOW UP PERIOD: Length of follow up was for duration of hospitalization

RESULTS:
Primary outcome: Preterm infants who received OMT in addition to usual care had a significant reduction of LOS compared to standard care/sham OMT (5 studies, n=1306; mean difference (MD) 2.7 days; 95% CI, -3.9 to -1.4).
Secondary outcomes: Preterm infants who received OMT had significantly lower costs compared to standard care/sham OMT (3 studies, n=915; MD -1545.66€; 95% CI, -1888.03€ to -1203.29€).
Subgroup analyses: Preterm infants who received OMT compared to standard care/sham OMT had significant reduction in LOS according to gestational age:

- < 32 weeks (2 studies, n=118; MD -8.6 days; 95% CI, -13.4 to -3.8).
- 32–35 weeks (3 studies, n=311; MD -3.1 days; 95% CI, -5.1 to -0.99).
- 35–37 weeks (3 studies, n=477; MD -2.2 days; 95% CI, -3.6 to -0.78 days).
- No adverse effects due to OMT reported.

LIMITATIONS:

- OMT not standardized by techniques, frequency, or length.
- High heterogeneity among included studies.
- No long-term follow-up of participants' respiratory or neurologic outcomes.
- Small sample sizes among sub-groups.

Brook Ashcraft, DO
Jeremy Ginoza, DO
Skagit Regional Health (Founding)
Mount Vernon, WA

Empagliflozin for diabetes, something to consider

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes: A Randomized Controlled Trial. *N Engl J Med* 2015; 373:21172128

KEY TAKEAWAY: In patients with type 2 diabetes at increased cardiovascular risk, empagliflozin 10 and 25mg added to standard care reduced all-cause mortality and a composite of cardiovascular outcomes compared to placebo.

STUDY DESIGN: Multicenter, randomized, double-blind, placebo-control trial (590 sites, 42 countries)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In the treatment of type 2 diabetes patients with increased cardiovascular risk, the effect of sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) on overall mortality and cardiovascular mortality is unknown. This study evaluated the SGLT-2 inhibitor, empagliflozin, in addition to standard diabetic care on cardiovascular outcomes.

PATIENTS: Type 2 diabetics at high risk for cardiovascular events; mean age 63 years, 71% male, 5% African-American; 75% coronary artery disease, 23% previous stroke, 20% peripheral arterial disease, 25% coronary artery bypass graft

INTERVENTION: Empagliflozin 10 mg or 25 mg PO daily

CONTROL: Placebo

OUTCOME: Primary outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcome: composite of the primary outcome plus hospitalization for unstable angina.

METHODS (BRIEF DESCRIPTION): Inclusion criteria of adults > 18 years, type 2 diabetes, BMI 45 or less, estimated glomerular filtration rate (eGFR) >30 ml/minute, hemoglobin A1c 7–9%, high cardiovascular risk (history of myocardial infarction, multi-vessel coronary artery disease (CAD), single vessel CAD with positive stress test, unstable angina with CAD evidence, stroke, occlusive peripheral artery disease), and no glucose lowering therapy for 12 weeks before randomization. Subjects randomized to either daily PO empagliflozin 10 mg or 25 mg or placebo plus standard care metformin (75%), insulin (53%), or sulfonylurea (43%). Median observation time 3.1 years.

INTERVENTION (# IN THE GROUP): 4687

COMPARISON (# IN THE GROUP): 2333

FOLLOW UP PERIOD: Median observation time 3.1 years, median treatment time 2.6 years

RESULTS:

- Primary composite outcome in pooled empagliflozin group significantly lower than placebo group (490/4687 (10.5%) vs 282/2333 (12.1%); hazard ratio (HR) 0.86; 95% CI, 0.74– 0.99; NNT 62).
- At 3.1 years follow-up there were lower rates of death from any cause in the pooled empagliflozin group compared to placebo (5.7% vs 8.3% ; relative risk reduction (RRR) 32%; P< 0.001; NNT 38), cardiovascular mortality (3.7 % vs. 5.9% ; RRR 38%; P<0.001; NNT 45), and hospitalization for heart failure (2.7% vs 4.1%; RRR 35%; P=0.002; NNT 71).
- Increased rate of genital infections in empagliflozin group vs placebo (6.4% vs 1.8%; P<0.001; number needed to harm (NNH) 22).

LIMITATIONS:

- Significant reductions in primary outcome only in certain subgroups, e.g., A1c <8.5%, age >65, etc.
- Primary outcome in the individual empagliflozin arms not statistically significant.
- Study funded by manufacturers of empagliflozin.

Nicholas Loughlin, DO
U of Wyoming FPRP – Casper (Founding)
Casper, WY

The Vaginal Microbiome and Preterm Birth: Is there a Relationship?

Meta-analysis of Vaginal Microbiome Data Provides New Insights into Preterm Birth

Kosti I, Gutierrez L, Lyalina S, Pollard K, Butte A, Sirota M. Meta-analysis of Vaginal Microbiome Data Provides New Insights into Preterm Birth. *Frontiers in Microbiology*. 2020; Volume 11: 476.

KEY TAKEAWAY: There is an association between vaginal microbiome variance and PTB, but clinically we do not know what to do with this information.

STUDY DESIGN: Meta-analysis of 5 prospective cohort studies

LEVEL OF EVIDENCE: STEP 3 (downgraded for lack of systematic review)

BRIEF BACKGROUND INFORMATION: Preterm birth (PTB), the birth of a child before 37 weeks of gestation, affects 12% of live births annually in the US. Low birth weight and prematurity are major contributors to infant mortality. There may be an association between vaginal microbiome variation and PTB, with conflicting outcomes in prior studies.

PATIENTS: Pregnant women

INTERVENTION: Vaginal microbiome sampling during different trimesters

CONTROL: N/A

OUTCOME: Preterm births

METHODS (BRIEF DESCRIPTION): Raw 16S sequence data from 5 cohort studies of pregnant women were uploaded into one shared database. The data were combined, processed using UPARSE, normalized, and modeled using linear mixed effects regression (LMER) to analyze with respect to birth timing as an outcome. Studies were excluded if they either only had processed date or lacked metadata and outcome information. All samples before 9 weeks and after 36 weeks were excluded to assure similar distributions of sampling in PTB and term cohorts: 1st Trimester (9-13 weeks); 2nd Trimester (14-25 weeks); 3rd Trimester (26-36 weeks). Relationship between race, bacterial genus', and birth timing were established. Experimental design and sampling strategies varied from study to study.

INTERVENTION (# IN THE GROUP): 415 pregnant women; 3,201 samples.

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: Until the end of pregnancy

RESULTS:

Across all trimesters, Lactobacillus was the only bacteria more abundant in women who deliver at term

In the first trimester, there were 6 bacterial genera associated with PTB:

- Olsenella ← novel association (known oral bacterial genus, reported in the past to be associated with BV but not PTB)
- Dialister
- Prevotella
- Megasphaera
- Lactobacillus
- Atopobium

In the second trimester, there was 1 bacterial genera associated with PTB:

- Lactobacillus

In the third trimester, there were 4 bacterial genera associated with PTB:

- Gardnerella
- Lactobacillus
- Aerococcus
- Clostridium sensu stricto ← novel association

LIMITATIONS: Since the lactobacillus findings are only at the genera level, further studies are needed to carry out species and strain level identification

Within-sample variance analysis is often used in gene expression analysis but not commonly employed in microbiome studies

- However, results were consistent with those of the original cohort studies

Variables often associated with PTB including medical conditions, prior pregnancy information, maternal age, periodontal disease, socioeconomic and education status, marriage status and maternal stress were not collected in the cohort data.

Ayanna Gouch, MD
Jamie Hill-Daniel, MD
MedStar Health/Georgetown-Washington Hospital Center FMRP
Washington, D.C.

Better Together: Treating Early Pregnancy Loss with Mifepristone AND Misoprostol

Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss

Schreiber C A, Creinin M D, Atrio J, et al. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. *N Engl J Med*. 2018; 378(23)

KEY TAKEAWAY: Pretreatment with mifepristone followed by treatment with misoprostol resulted in a higher likelihood of successful management of early pregnancy loss than with misoprostol alone.

STUDY DESIGN: Multisite, single blind randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Misoprostol for management of early pregnancy loss is popular among women looking to avoid surgical management. Unfortunately, a single vaginal dose of 800mg misoprostol is often ineffective in women with a closed cervix, often requiring a second dose. Mifepristone used as a pretreatment to the misoprostol dose may increase the efficacy of this management strategy.

PATIENTS: Women 18 years and older with an ultrasound (US) confirmed nonviable intrauterine pregnancy (IUP) between 5 and 12 weeks of gestation

INTERVENTION: Women 18 years and older with an ultrasound (US) confirmed nonviable intrauterine pregnancy (IUP) between 5 and 12 weeks of gestation

CONTROL: Misoprostol 800 mg vaginally

OUTCOME: complete expulsion of gestational sac 1-4 days after misoprostol administration.

METHODS (BRIEF DESCRIPTION): Women 18 years or older with US confirmed non-viable IUP at 5-12 weeks gestation were randomized to receive either:

- 200 mg Mifepristone on day 1 then 800mg Misoprostol vaginally 24hrs later
- Misoprostol 800mg vaginally on day 1.

At Day 3, blinded investigators assessed outcome with endovaginal US. If the gestational sac was completely expelled, this was considered treatment success.

If gestational sac was still present, women were offered a 2nd dose of misoprostol or expectant/surgical management. These women were followed up on Day 8 (5 days later) for a second blind evaluation.

All participants were contacted 30 days after initial randomization to assess side effects (scored on a Likert scale from 1 (lowest) to 5 (highest) as well as acceptability of the treatment.

INTERVENTION (# IN THE GROUP): 149

COMPARISON (# IN THE GROUP): 151

FOLLOW UP PERIOD:

- 30 days total
- 1-4 days for first follow up
- Additional 5 days for second follow up

RESULTS:

- Primary Outcome:
  - Day 3 - complete expulsion of gestational sac favored combination treatment.
    - RR 1.25; 95% CI, 1.09–1.43
    - NNT = 6
- Secondary Outcomes:
  - Day 8: complete expulsion of gestational sac favored combination treatment:
    - RR 1.23; 95% CI, 1.10–1.39.
    - NNT = 7
  - Day 30: cumulative rate of complete expulsion with up to 2 doses of misoprostol favored combination treatment:
    - RR 1.20; 95% CI, 1.08–1.33
  - Fewer women receiving combination treatment required uterine aspiration:
    - RR 0.37; 95% CI, 0.21–0.68.
  - Side effects and acceptability:
    - No significant differences

LIMITATIONS: Patients were not blinded to the treatment (No mifepristone placebo was administered to the misoprostol only group) which may have led to biased reporting of side effects and acceptability.

Liseli James, MD
Jamie Hill-Daniel, MD
MedStar Health/Georgetown-Washington Hospital Center FMRP
Washington, D.C.

Hypertonic Dextrose Prolotherapy Effective in Decreasing Knee Osteoarthritis Pain

Efficacy of Intra-Articular Hypertonic Dextrose (Prolotherapy) for Knee Osteoarthritis: A Randomized Controlled Trial

Sit R, Wu R, Rabago D, et al. (2020). Efficacy of Intra-Articular Hypertonic Dextrose (Prolotherapy) for Knee Osteoarthritis: A Randomized Controlled Trial. *Annals of Family Medicine*, 18(3), 235–242.

KEY TAKEAWAY: Intra-articular hypertonic dextrose injections reduce pain from knee osteoarthritis compared to normal saline, although the reduction may not be clinically meaningful.

STUDY DESIGN: Double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Osteoarthritis, a prevalent condition, has many treatment options, many of which have adverse effects and only provide short term pain relief. This study tests the effects of intra-articular injection of hypertonic dextrose to provide long term pain relief and improve joint function and stiffness over a year.

PATIENTS: Adults 45-76 years old with symptomatic knee osteoarthritis

INTERVENTION: Intra-articular 25% dextrose administered at weeks 0, 4, 8, and 16

CONTROL: Intra-articular normal saline

OUTCOME: Change in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index, (scale 0–100, with higher scores indicating more pain. A change of > 12 points is considered meaningful)

METHODS (BRIEF DESCRIPTION): This double blind, randomized controlled trial, conducted in Hong Kong, enrolled 76 patients between 45-75 years old, who met the inclusion criteria of moderate to severe pain for at least 3 months, BMI <35, and failure of pain control via conservative care. Patients received either 5mL of 25% dextrose or 5mL of normal saline in the affected knee joint at weeks 0, 4, 8, and 16. The primary and secondary outcomes were set for pain control, function, and stiffness, and were measured using the WOMAC Index (0-100 points) at weeks 16, 26, and 52.

INTERVENTION (# IN THE GROUP): 38

COMPARISON (# IN THE GROUP): 38

FOLLOW UP PERIOD: 16, 26, and 52 weeks.

RESULTS:

For the primary outcome of pain control, the WOMAC score at 52 weeks was lower in the intra-articular hypertonic dextrose group compared to intra-articular normal saline: -10.34 (95% CI, -19.20 to -1.49, P = 0.022). The secondary outcomes involved the WOMAC function and stiffness scores. The results at 52 weeks were statistically significant for function: -9.55 (95% CI, -17.72 to -1.39), but not significant for stiffness. Another secondary outcome was objective assessment of function, measured with a 30-second chair stand and a 40-meter fast-paced walk. The 30-second chair stand was measured as the maximum number of chair stand repetitions in a 30-second period, while the 40-meter fast-paced walk was evaluated as a timed event. The results for both evaluations were not significant. While the results were statistically significant for pain control and function at week 52, they were not significant immediately at the end of the injection series at week 16. The WOMAC pain score difference at week 16 was: -4.81 (95% CI: -13.47 to 3.85), while the function was reported at: -4.50 (95% CI: -12.49 to 3.49). It was not until week 26 and beyond when the outcomes for pain and function diverged. Although the results were statistically significant, they may not have been clinically important as the WOMAC index difference was not greater than 12 points in any of the evaluated outcomes.

LIMITATIONS:

- Not controlling for exercise and weight loss during the testing period was a limitation that could have confounded the results of the study.
- The study also does not account whether the patients attempted other treatment modalities during the 52-week trial period.
- The primary outcome did not reach the clinical importance threshold. The study also did not compare results to the usual care options (i.e. acetaminophen, hyaluronic acid, corticosteroids).

Faizan Memon, MD
CMU College of Medicine
Saginaw, MI