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A Ringing Endorsement is Lacking

Faster Discharge with Lactated Ringers than Normal Saline in First 72 Hours of Acute Pancreatitis: A Multicenter Randomized Trial

Farrell PR, DesPain AW, Farmer P, et al. Faster discharge with lactated ringers than normal saline in first 72 h of acute pancreatitis: A multicenter randomized trial. *J Pediatr Gastroenterol Nutr*. 2024;78(2):360-368. doi:10.1002/jpn3.12082

KEY TAKEAWAY: Compared with normal saline (NS), lactated Ringer's (LR) did not significantly decrease C-reactive protein (CRP) levels at 24 or 48 hours in pediatric patients with acute pancreatitis (AP).

STUDY DESIGN: Randomized, multicenter, controlled trial

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

BRIEF BACKGROUND INFORMATION: Isotonic fluids are traditionally used to manage pediatric AP, but it is unknown if LR might provide benefits over NS. Adult studies suggest LR may be better, but findings are inconsistent, and pediatric data lacked.

PATIENTS: Pediatric patients with AP

INTERVENTION: Hydration with LR solution

CONTROL: Hydration with NS

PRIMARY OUTCOME: CRP levels

Secondary Outcome: Length of stay (LOS), time to initiation of feeds, changes in biochemical markers, development of systemic inflammatory response syndrome (SIRS), progression to severe acute pancreatitis (SAP)

METHODS (BRIEF DESCRIPTION):

- Pediatric patients <19 years old diagnosed with their first episode of AP were included in the study.
- The diagnosis of AP was based on the presence of at least two of the following:
  - Abdominal pain consistent with pancreatitis
  - Elevated amylase and/or lipase (≥3 times the upper limit of normal)
  - Imaging findings indicating pancreatic inflammation
- Patients with prior AP episodes or conditions preventing aggressive fluid hydration were excluded from the study.
- Patients were assigned to receive either LR or NS.
- Fluid resuscitation was initiated within six hours of diagnosis at 1.5 times the maintenance rates (Holiday-Segar method).
  - Additional resuscitation fluids (boluses) were recorded if given.
- The primary outcome measured the changes in CRP levels at admission, 24 hours, and at 48 hours.
- The secondary outcomes measured the LOS; time to initiation of feeds; changes in biochemical markers which included blood urea nitrogen (BUN), amylase, and lipase; development of SIRS; and progression to SAP.

INTERVENTION (# IN THE GROUP): 38

COMPARISON (# IN THE GROUP): 38

FOLLOW-UP PERIOD: 72 hours

RESULTS:

Primary Outcome –

- There was no significant difference between LR and NS CRP levels at 24 or 48 hours.
  - 24 hours (2.1 vs 1.9 mg/dL, respectively; p=.70)
  - 48 hours (2.9 vs 1.8 mg/dL, respectively; p=.33)

Secondary Outcome –

- There was no significant difference between LR and NS for LOS, time to initiation of feeds, changes in the biochemical markers of BUN, amylase or lipase, development of SIRS, or progression to SAP at 24 hours.
- There was no significant difference between LR and NS for LOS, time to initiation of feeds, changes in the biochemical markers of BUN, amylase or lipase, development of SIRS, or progression to SAP at 48 hours.
- BUN values were significantly higher in the LR group at 48 hours compared to the NS group (6 vs 4 mg/dL, respectively; p=.02).

LIMITATIONS:

- The study included a small sample size, which may limit the generalizability of findings.
- Only LR and NS were compared, without assessing other potential fluid resuscitation strategies.
- Treatment teams were aware of fluid assignments, which may have influenced clinical decisions.
- The study was conducted across multiple institutions, where differences in discharge criteria and treatment approaches may have impacted LOS outcomes.
- The study focused on short-term outcomes (72-hour discharge and LOS) without long-term follow-up on disease progression or recurrence.
- Patients with prior pancreatitis or underlying chronic illnesses were excluded, limiting applicability to broader pediatric populations.

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Triple Combination Treatment for Moderate-to-Severe Acne

Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination

Stein Gold L, Baldwin H, Kircik LH, et al. Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug. *Am J Clin Dermatol*. 2022;23(1):93-104. doi:10.1007/s40257-021-00650-3

KEY TAKEAWAY: Once-daily gel containing benzoyl peroxide, clindamycin, and adapalene improves moderate-to-severe acne symptoms more than two-ingredient gels or control after 12 weeks.

STUDY DESIGN: Double-blind, parallel-group, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Acne is a commonly diagnosed condition in primary care. There are many available treatment options, with patients often receiving prescriptions for multiple agents. This study investigated the effectiveness of a new combination of gel containing three common topical acne treatments.

PATIENTS: Patients with moderate-to-severe acne

INTERVENTION: Triple-ingredient topical gel (IDP-126)

CONTROL: Topical two-ingredient gels or a control gel

PRIMARY OUTCOME: Treatment success and number of inflammatory and non-inflammatory lesions

Secondary Outcome: Medication safety and tolerability

METHODS (BRIEF DESCRIPTION):

- Patients ≥9 years old, diagnosed with moderate-to-severe acne with both inflammatory and non-inflammatory lesions were included in the study.
- Patients with >2 nodules were excluded from the study.
- Investigators selected patients from multiple centers in the United States and Canada and randomized them to one of four treatment groups or a control group.
- IDP-126 was comprised of benzoyl peroxide 3.1% (BPO), clindamycin 1.2% (Clin), and adapalene 0.15% (ADAP).
- The control group was comprised of three two-ingredient gels: BPO/ADAP, Clin/BPO, and Clin/ADAP at the same strength and in the same vehicle.
    - The control gel consisted of the vehicle without any active ingredients.
- Investigators instructed all participants to apply the gel once daily for 12 weeks and use the same facewash, lotion, and sunscreen.
- Investigators defined treatment success as acne severity score improvement by at least two points and with a total score of zero or one using the Evaluator's Global Severity Score (EGSS) after 12 weeks.
    - The EGSS scores range from 0–5, with higher scores indicating increased acne severity.
- Investigators also determined the reduction in the number of inflammatory and non-inflammatory lesions at 12 weeks.

INTERVENTION (# IN THE GROUP): 147

COMPARISON (# IN THE GROUP):

- BPO/ADAP: 150
- Clin/BPO: 146
- Clin/ADAP: 150
- Vehicle gel: 148

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- IDP-126 improved treatment success compared to BPO/ADAP, Clin/BPO, Clin/ADAP, and control (53%, 28%, 31%, 30%, and 8.1%, respectively; $p<.0001$).
- IDP-126 significantly reduced the number of inflammatory acne lesions compared to BPO/ADAP, Clin/BPO, Clin/ADAP, and control (–76%, –68%, –64%, –69%, and –50%, respectively; $p<.0001$).
- IDP-126 significantly reduced the number of non-inflammatory acne lesions compared to BPO/ADAP, Clin/BPO, Clin/ADAP, and control (–71%, –61%, –59%, –61%, and –46%, respectively; $p<.0001$).

Secondary Outcome –

- <6% of participants in any intervention group had a severe rating on any cutaneous safety or tolerability assessment.

LIMITATIONS:

- The study population was limited to patients with moderate-to-severe acne, a majority of whom were white and female.
- The study looked at the effects of treatment over only 12 weeks.
- Researchers did not investigate the effects of different dosages of the three ingredients included in the topical gel.
- The acne severity scoring system used in the study had the potential to introduce bias and/or variation between researchers into the data.
- Adherence to the regimen may have varied across the treatment groups.

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Shocking News: Are Two Shocks Better Than One?

Defibrillation Strategies for Refractory Ventricular Fibrillation

Cheskes S, Verbeek PR, Drennan IR, et al. Defibrillation Strategies for Refractory Ventricular Fibrillation. *N Engl J Med*. 2022;387(21):1947-1956. doi:10.1056/NEJMoa2207304

KEY TAKEAWAY: Double sequential external defibrillation (DSED) and vector change (VC) defibrillation strategies improve survival to hospital discharge compared to standard defibrillation (SD) in patients with refractory ventricular fibrillation (VF) during out-of-hospital cardiac arrest.

STUDY DESIGN: Three group, cluster randomized controlled trial with crossover

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Out-of-hospital cardiac arrests account for 350,000 deaths each year in North America. Almost 100,000 of these cardiac deaths are attributed to VF or pulseless ventricular tachycardia. Roughly half of these patients remained in VF despite SD. This study aimed to investigate if DSED or VC defibrillation techniques would increase survival to hospital discharge in out-of-hospital cardiac arrests that are experiencing VF.

PATIENTS: Adult patients with refractory VF during out-of-hospital cardiac arrest

INTERVENTION: DSED or VC

CONTROL: SD

PRIMARY OUTCOME: Survival to hospital discharge
Secondary Outcomes: Termination of VF, return of spontaneous circulation (ROSC), neurological outcomes at hospital discharge

METHODS (BRIEF DESCRIPTION):

- Patients ≥18 years old who had out-of-hospital VF arrest of presumed cardiac cause and refractory VF (VF unresponsive after three rhythm checks and SDs) were included in the study.
- Patients with non-VF as presenting rhythm, non-cardiac cause, traumatic cardiac arrest, drowning, hypothermia, hanging, suspected drug overdose, do not resuscitate order, patients treated by non-participating fire or emergency medical services (EMS) agencies were excluded from the study.
- Six paramedic groups of roughly 4,000 paramedics were randomly assigned to one of three treatment groups which included DSED, VC, or SD.
  - Each paramedic group would crossover treatment groups every six months so that each paramedic group had to cross over to each of the treatment groups at least once throughout the study.
- Patients with refractory VF were randomized into three groups: DSED, VC, or SD based on the paramedic group responding to the call.
  - Each rhythm analysis occurred at standard two-minute intervals.
- For all patients, the first three defibrillation attempts were given using SD pad placement. Further defibrillation attempts were given according to the paramedic group of which the patient had been assigned (DSED, VC, or SD).
- The primary outcome measured the survival to hospital discharge.
- The secondary outcomes measured termination of ventricular fibrillation, ROSC, and good neurological outcomes measured defined as a score of ≤2 on the Modified Rankin scale (mRs).
  - The mRs is a six-point scale used to assess disability with a score of one meaning no significant disability. A score of six is death.
- The primary statistical analysis used an intention-to-treat model and adjusted relative risks.
  - Results were adjusted for age, sex, bystander cardiopulmonary resuscitation (CPR), and clustering effects.

INTERVENTION (# IN THE GROUP): 269

COMPARISON (# IN THE GROUP): 136

FOLLOW-UP PERIOD: Until hospital discharge or death

RESULTS:

Primary Outcome –

- Patients who received DSED were more likely to survive to hospital discharge compared to those who received SD (adjusted relative risk [ARR] 2.2; 95% CI, 1.3–3.7).
- Patients who received VC were more likely to survive to hospital discharge compared to those who received SD (ARR 1.7; 95% CI, 1.01–2.9).

Secondary Outcome –

- Patients who received DSED were more likely to achieve termination of VF compared to SD (ARR 1.3; 95% CI, 1.1–1.4).
- Patients who received DSED were more likely to achieve ROSC compared to SD (ARR 1.7; 95% CI, 1.2–2.4).
- Patients who received DSED were more likely to achieve a mFs score ≤2 compared to SD (ARR 2.2; 95% CI, 1.3–3.9).
- Patients who received VC were more likely to achieve termination of VF compared to SD (ARR 1.2; 95% CI, 1.03–1.4).
- Patients who received VC did not have a significant difference in ROSC or mFs score of ≤2 compared to SD.

LIMITATIONS:

- The study ended early due to challenges related to COVID-19.
- The primary outcome had a small number of events, which may have led to overestimation of the effect size.
- Length of in-hospital stay distributions are not known. Modified Rankin score could be lower for DSED patients since they had longer recovery times in the hospital.
- The generalizability of the findings to rural settings is uncertain, as the majority of patients were enrolled in urban settings. EMS services in rural areas may not have access to two defibrillation devices.
- Potential confounding factors such as patient demographics, past medical history, patient home medications, and in-hospital interventions were not accounted for in the analysis.
- Treatment group was known throughout patients' hospitalization. Clinicians may have treated patients differently if they knew that the patient was in the treatment group compared to the placebo group.

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Risky Doses? PRN Medication Effects on Blood Pressure and End Organ Damage in Hospitalized Veterans

As-Needed Blood Pressure Medication and Adverse Outcomes in VA Hospitals

Canales MT, Yang S, Westanmo A, et al. As-Needed Blood Pressure Medication and Adverse Outcomes in VA Hospitals. *JAMA Intern Med*. 2025;185(1):52-60. doi:10.1001/jamainternmed.2024.6213

KEY TAKEAWAY: As-needed blood pressure (BP) medication administration increases the risk of developing an acute kidney injury (AKI) compared to scheduled BP medication administration in hospitalized veterans.

STUDY DESIGN: Multicenter retrospective cohort study with target trial emulation

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: As-needed medications are commonly used to reduce elevated BP quickly in the hospital though they can lead to adverse events. No definite consensus has been reached to determine if the harm outweighs the benefits, especially in a vulnerable cohort, such as veterans. This study aimed to assess the effects of as-needed BP medication on hospitalized veterans to contribute further to the debate between risks and benefits of acute BP reduction.

PATIENTS: Hospitalized veterans on non-intensive care unit (ICU), non-surgical floors

INTERVENTION: As-needed BP medication

CONTROL: Scheduled BP medication

PRIMARY OUTCOME: Time to AKI event

Secondary Outcome: Rapid BP drop, composite incidence of myocardial infarction (MI), stroke, or death

METHODS (BRIEF DESCRIPTION):

- Adult veterans hospitalized on medical or surgical floors for a minimum of three days with elevated BP were included in the study.
- Those who did not receive scheduled BP medication or had known diagnoses that would necessitate use of BP medication were excluded from the study.
- A target trial emulation approach was used to compare those who received ≥1 as-needed BP medication with those who only received scheduled BP medication.
    - As needed referred to recurring or one-time orders of oral or intravenous (IV) antihypertensive of any class when the systolic BP was >140 mmHg.
    - Scheduled antihypertensives orders were placed in response to a systolic BP >140 mmHg to remain part of the daily medication regimen.
- Route of administration and specific drug were not factors in the determination of groups.
- The primary outcome measured the first occurrence of an AKI event and was assessed following administration of a BP medication using the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI and data records for baseline creatinine assessment.
- Secondary outcomes were measured in the following ways:
    - Rapid drop in BP was defined as 25% reduction within 1–3 hours following medication administration if vitals available in the window.
    - Discharge diagnosis codes were used to ascertain the occurrence of MI, stroke, or death during hospitalization.

INTERVENTION (# IN THE GROUP): 28,526

COMPARISON (# IN THE GROUP): 105,234

FOLLOW-UP PERIOD: Within hospital stay

RESULTS:

Primary Outcome –

- As-needed BP medication increased the risk of AKI compared to those on a scheduled BP medication regimen (hazard ratio [HR] 1.2; 95% CI, 1.2–1.3).

Secondary Outcome –

- As-needed BP medication increased the risk of a rapid drop in BP within the first one hour compared to those on a scheduled BP medication (HR 2.11; 95% CI, 1.8–2.5)
- As-needed BP medication increased the risk of a rapid drop in BP within the first three hours compared to those on a scheduled BP medication (HR 1.5; 95% CI, 1.4–1.6).
- As-needed medication significantly increased the risk of composite MI, stroke, or death compared to a scheduled BP medication regimen (rate ratio [RR] 1.7; 95% CI, 1.5–1.9).

LIMITATIONS:

- There is a lack of generalizability due to a mostly White male patient population.
- Only 3% of the as-needed medications given were orally.
- The possibility of confounding variables cannot fully be excluded despite propensity score matching; therefore, causality cannot be certain.
- Some patients may have symptoms necessitating use of as-needed medication, like arrhythmias or alcohol withdrawal.

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Role of PTSD in Type 2 Diabetes Complications

Posttraumatic Stress Disorder and Type 2 Diabetes Outcomes in Veterans

Scherrer JF, Salas J, Wang W, et al. Posttraumatic Stress Disorder and Type 2 Diabetes Outcomes in Veterans. *JAMA Netw Open*. 2024;7(8):e2427569. Published 2024 Aug 1. doi:10.1001/jamanetworkopen.2024.27569

KEY TAKEAWAY: Among Veterans 18–80 years old with comorbid post-traumatic stress disorder (PTSD) and type 2 diabetes mellitus (T2DM), those who no longer meet PTSD criteria have a lower risk of microvascular complications compared to those with persistent PTSD. However, they do not differ in rates of insulin initiation, poor glycemic control, or all-cause mortality.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Patients with PTSD face shorter life expectancies, in part due to associations with poor metabolic health, including a significantly higher risk of T2DM. This study aimed to investigate whether improvement in PTSD symptoms in Veterans with comorbid T2DM reduces the risk of adverse diabetes outcomes.

PATIENTS: Patients 18–80 years old with comorbid PTSD and T2DM

INTERVENTION: Decreased PTSD severity

CONTROL: Persistent PTSD severity

PRIMARY OUTCOME: T2DM microvascular complications, insulin initiation, poor glycemic control, and all-cause mortality

METHODS (BRIEF DESCRIPTION):

- A cohort study used deidentified data from the US Veterans Health Administration (VHA) medical records from 2012–2022.
- Adults with PTSD, defined as a PTSD Checklist (PCL) score of ≥ 33 and a T2DM diagnosis were followed for 2–9 years based on when they met eligibility criteria were included in the study.
    - Scores on the PCL range from 0–80, with scores >31–33 corresponding to a provisional diagnosis of PTSD and higher scores indicating more functional impact of symptoms.
- Patients with insulin use, microvascular complications, type 1 diabetes mellitus (T1DM) diagnosis HbA1c >7.5%, and missing demographic data at the start of the study were excluded from the study.
- The intervention included patients with decreased PTSD severity defined as a PCL score of <33 within the index year.
- The control group included patients with persistent PTSD defined as a PCL score >33.
- The following were measured as the primary outcomes:
    - T2DM microvascular complications were defined as the presence of ICD-9 or ICD-10 codes for diabetic nephropathy, retinopathy, or neuropathy.
    - Insulin initiation was identified through pharmacy records documenting the prescription for insulin therapy.
    - Poor glycemic control was defined as HbA1c ≥7.5%.
    - All-cause mortality was measured using the VHA master file, which included dates of patient death.
- Entropy balancing was used to control for confounding by removing differences in the distribution of covariates between patients with persistent PTSD and those who no longer met PTSD criteria.
- Hazards ratios and confidence intervals were calculated to determine the risk of adverse T2DM outcomes between the two comparison groups before and after entropy balancing.

INTERVENTION (# IN THE GROUP): 2,124

COMPARISON (# IN THE GROUP): 7,878

FOLLOW-UP PERIOD: 2–9 years

RESULTS:

Primary Outcome –

- Patients no longer meeting PTSD criteria had a decreased risk of microvascular complications compared to patients with persistent PTSD (hazard ratio [HR] 0.92; 95% CI, 0.85–0.99).
- Patients no longer meeting PTSD criteria did not have an increased risk of starting insulin compared to patients with persistent PTSD (HR 0.93; 95% CI, 0.80–1.1).
- Patients no longer meeting PTSD criteria did not have worse glycemic control compared to patients with persistent PTSD (HR 1.00; 95% CI, 0.93–1.1).
- Patients no longer meeting PTSD criteria did not have different rates of all-cause mortality compared to those with persistent PTSD (HR 0.99; 95% CI, 0.79–1.2).

LIMITATIONS:

- The study did not measure how long patients had PTSD and T2D prior to the start of the study, which could affect the results.
- Results are based on data from the VHA and may not generalize to other health systems or patient populations.
- There is a risk of misclassification of undiagnosed microvascular complications, which may have biased the results toward finding no effects.
- Majority of the study's participants are male, which may limit the generalizability of results to female patients.
- While a PCL score of 33 has strong internal consistency and validity, it is not a definitive diagnosis as it is based on a questionnaire rather than a clinical diagnosis.

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