Management of Bleeding & Coagulopathies: A Primer for Pharmacists

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Disclosure

• No conflicts of interest
Learning Objectives

• List common causes of bleeding in the critically ill patient
• Compare and contrast the safety and efficacy of blood and factor products used to control bleeding
Outline

• **Part I**
  ▪ Assessment of hemostasis

• **Part II**
  ▪ Overview of commonly used blood products

• **Part III**
  ▪ Pharmacologic agents
Coagulation Cascade

**Intrinsic System**
- Endothelium Damage

**Extrinsic System**
- Tissue Damage

**Common Pathway**
- Collagen
- XII → XI → IX → VIII → X
- Thrombin
- Prothrombin (II) → Fibrinogen (I)
- Fibrin Clot → Platelets
Measures of Coagulopathy

- **Activated Partial Thromboplastin Time (aPTT):** intrinsic pathway
- **Prothrombin Time (PT):** extrinsic pathway

<table>
<thead>
<tr>
<th>PT</th>
<th>aPTTT</th>
<th>Coagulation Pathway Abnormality</th>
<th>Causes of Prolongation</th>
</tr>
</thead>
</table>
| Prolonged   | Normal| Extrinsic pathway               | • Factor VII deficiency  
• Mild Vitamin K deficiency  
• Mild hepatic deficiency  
• Vitamin K antagonist administration |
| Normal      | Prolonged| Intrinsic pathway               | • Factor VIII, IX, XI, XII deficiency  
• Heparin administration  
• Direct thrombin inhibitor administration  
• Anti-phospholipid syndrome |
| Prolonged   | Prolonged| Common pathway                 | • Global clotting factor deficiency  
• Factor Xa inhibitor administration  
• Vitamin K antagonist administration |
International Normalized Ratio (INR)

- Developed for warfarin therapy monitoring
  - Accounts for variations in laboratories (source of thromboplastin and instrument used to measure)
  - Sensitive to vitamin K-depending clotting factors (VII, X, II)
  - Insensitive to factor IX, protein C and S

- Commonly used as a surrogate for PT
  - Assesses extrinsic and common pathways
  - Limitations (ESLD, lupus anticoagulant, etc.)

\[
\text{INR} = \left( \frac{\text{PT}_{\text{Test}}}{\text{PT}_{\text{Normal}}} \right)_{\text{ISI}}
\]
# Causes of Hemostatic Alterations

## Coagulopathy
- Hypothermia
- Acidosis
- Dilutional
- Disseminated intravascular coagulation (DIC)
- Hepatic dysfunction
- Renal dysfunction
- Inherited abnormalities
- Medications

## Thrombocytopenia
- Cancer
- Intravascular devices
- Infections
- Sepsis
- Disseminated intravascular coagulation (DIC)
- Hepatic dysfunction
- Immune-mediated
- Medications
Goals of Therapy

• Stop or control hemorrhage
• Minimize blood product use
• Minimize adverse events
• Correct coagulation tests and blood counts
• Achieve pH ≥ 7.2, temperature ≥ 35°C, normal ionized calcium
Overview of Management Principles

• Early identification of bleeding sources and prompt measures to minimize blood loss

• Management of hemorrhagic shock by restoring blood volume
  ▪ Restore adequate end-organ perfusion
  ▪ Increase oxygen carrying capacity of the circulating blood
  ▪ Achieve hemodynamic stability
  ▪ Reverse hypocoagulable state

• Damage control resuscitation
  ▪ Rapid hemorrhage control through early administration of blood products in a balanced ratio to closely mimic “whole blood”
    o Red blood cells (RBCs), plasma (FFP), and platelets in a set ratio (1:1:1)
Blood Products
Part II
Blood Products - Overview

- Whole Blood
- PRBC
- Plasma
- Cryoprecipitate
- Platelets

Clotting factors

Oxygen-carrying capacity

Fibrin
Whole Blood

• Collected in bags containing citrate-phosphate-dextrose-adenine (CPDA) solution
  - Citrate chelates the calcium present in blood and prevents coagulation
  - Centrifuged down to PRBCs, FFP, platelets, and cryoprecipitate
  - Shelf life = 35 days

• Potential complications:
  - Metabolic alkalosis
    ▪ Citrate converted to bicarbonate
  - Decreased ionized calcium
    ▪ Binding of calcium and citrate
Packed Red Blood Cells (PRBCs)

• **Indication:**
  - Treatment of symptomatic anemia
  - Prophylaxis in life-threatening anemia
  - Restoration of oxygen-carrying capacity in case of hemorrhage

• **Preparation:** prepared by centrifugation of whole blood

• **Content:** red blood cells (Hct 55-65%)

• **Storage:**
  - Refrigerated
  - Shelf-life 42 days
  - Preservatives added to extend shelf-life
Packed Red Blood Cells (PRBCs)

• **Dose:** 1 unit (300 ml) typically elevates Hgb by roughly 1 g/dL
• **Onset:** Measure Hgb 15 minutes after transfusion
• **Clinical Pearls:**
  - **Metabolic Alkalosis**
    - Solution is stored at pH value of 6.7 (sodium citrate, citric acid)
      - 1 mmol citrate $\rightarrow$ 3 mEq bicarbonate
  - **Hypocalcemia**
    - Citrate added to chelate calcium and prevent coagulation
      - Calcium gluconate 1-2g per 2 units PRBC
  - **Potassium leakage**
    - Typically shifts intracellularly or excreted in urine (no net increase)
    - Highest risk of hyperkalemia in trauma, renal impairment and infants

American National Red Cross 2015
PRBCs: The Risks

- **Infectious**
  - HIV (1 in 1,467,000)
  - Hepatitis C (1 in 1,149,000)
  - Hepatitis B (1 in 282,000)
  - Cytomegalovirus (50-85% donors are carriers)
  - Bacterial (1 in 2,000 – more common with platelets)
  - Parasitic (uncommon)

- **Immunological**
  - TACO (Transfusion Associated Circulatory Overload)
  - TRALI (Transfusion Related Acute Lung Injury)
  - TRIM (Transfusion Related Immunomodulation)

- **Allergic**
  - Anaphylactic/
# Transfusion Thresholds: Overview

*Restrictive > Liberal*

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Hemoglobin Threshold</th>
<th>Evidence Quality</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU patients</td>
<td>≤ 7 g/dL</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Trauma</td>
<td>≤ 7 g/dL</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Acute hemorrhage</td>
<td>NA</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>No recommendation</td>
<td>Very Low</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>≤ 8 g/dL or for symptoms</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>Post-operative</td>
<td>≤ 8 g/dL or for symptoms</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
</tbody>
</table>

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Fresh Frozen Plasma (FFP)

• **Preparation**: plasma that is separated from the red blood cell component of whole blood by centrifugation

• **Content**: coagulation factors, fibrinogen (1-2.5 mg/ml), albumin, proteins C and S

• **Indications**: correction of coagulopathy
  - Elevated PT/INR or aPTT

• **Storage**: frozen to reserve labile clotting factors
  - Thawed (takes 30 minutes) prior to administration
  - Stable for 4 days once thawed

Gunter Anesthesiology 1996; 85: 1219-1220
Voils S. Pharmacotherapy 2007; 27: 69-84
Shander A et al. Pharmacotherapy 2007; 27: 57-68
Fresh Frozen Plasma (FFP)

• **Dose:** 10 - 15 ml/kg
  - Will restore coagulation factors to 30% of baseline (1 unit = 200-250 ml)
  - MUST have sufficient fibrinogen for effect (fibrinogen >80-100 mg/dL)

• **Adverse effects:** TRALI, TACO, infection transmission, thromboembolic effects, transfusion related side effects

• **Clinical Pearls:**
  - Typically stored “unthawed” in large trauma centers
  - Large volumes (15 ml x 80 kg = 1200 ml) may be problematic in patients with preexisting renal, cardiac, and pulmonary disorders
  - Solution contains citrate and may cause hypocalcemia
  - Inherent INR ~ 1.3
Cryoprecipitate

• **Preparation:** centrifugation of 1 unit of whole blood; insoluble precipitate is reconstituted with 20-40 ml of plasma to yield cryoprecipitate

• **Content:** fibrinogen (15-25 mg/ml), Von Willebrand Factor (vWF), Factors VIII and XIII

• **Indications:** fibrinogen < 100 mg/dL
  - Dysfibrigenemia

• **Storage:** frozen
  - Stable for 12 months
Cryoprecipitate

**Dose:** Replete as needed for fibrinogen level <100 mg/dL or suspected dysfibrinogenemia
- 1 unit should increase fibrinogen by 5-10 mg/dL
- “Pool” = 5 units

**Complications:** infection transmission, thromboembolic effects, transfusion related side effects

**Clinical Pearls:**
- No antibody testing necessary
- Small volume (<100 ml)
Platelets

• **Preparation:** repeated centrifugation of whole blood to make a concentrated form of platelets

• **Contents:**
  - $>5.5 \times 10^{10}$ platelets suspended in roughly 50 ml of plasma

• **Indications:** thrombocytopenia
  - Optimal platelet count to prevent bleeding or to maintain during hemorrhage is not well established
  - Bleeding risk is minimal if platelets $> 50 \times 10^9$/L

• **Storage:** room temperature
  - Stable for 5 days; circulating platelets have short half life
  - Stored using continuous agitation
Platelets

- **Dose**: dosing is typically done in “six packs” – should raise platelets by 25-50 x 10^9/L within 1 hour of transfusion
  - Administered in a fixed ratio with RBCs and FFP

- **Complications**: transfusion-related sepsis with bacterial contamination of stored platelets at room temperature

- **Clinical Pearls**:
  - “Six pack” = 250-350 ml
Pharmacologic Agents
Part III
Factor Products - Overview

• Factor Products
  • Factor Content
  • Mechanism
• Assessment of appropriate use
  • Indications
  • Factor Stewardship Programs
• Patient-specific considerations
  • Platelets, PT/INR, Fibrinogen, pH, body temperature
  • Thromboembolic risks
• Dosing
  • Efficacy
# Factor Products: Summary

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>Factor Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VII</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>NovoSeven®</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>(activated)</td>
<td></td>
</tr>
<tr>
<td>3-Factor PCC</td>
<td>Bebulin VH®</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Profilnine SD®</td>
<td></td>
</tr>
<tr>
<td>4-Factor PCC</td>
<td>Kcentra®</td>
<td>✓</td>
</tr>
<tr>
<td>Activated PCC</td>
<td>FEIBA®</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>(activated)</td>
<td></td>
</tr>
</tbody>
</table>

PCC = Prothrombin Complex Concentrate
Coagulation Cascade

Intrinsic System

Extrinsic System

Endothelium Damage

Tissue Damage

Collagen

XII

XI

IX

VIII

X

V

Ca^{2+}

Thrombin

Fibrinogen

XII

VII

VIIa

Tissue Factor

Promotes factor X activation and thrombin generation

Increased activity of the extrinsic system

Binds to platelet surfaces

4F-PCC

Fibrin Clot

Platelets


# Role of rFVIIa to Enhance Hemostasis

## Indications

- **FDA-Approved:**
  - Hemophilia A or B
  - Acquired Hemophilia
  - Congenital factor VII deficiency,
  - Glanzmann’s thrombasthenia

- **Off-Label:**
  - Intracranial hemorrhage
  - Cardiac surgery
  - Trauma-related coagulopathy
  - Refractory perioperative bleeding
  - Liver disease

## Comparison to Blood Products

- **Advantages**
  - Rapid administration
  - Significantly less fluid volume
  - Avoidance of blood exposures

- **Disadvantages**
  - Lack of evidence for use
  - Thromboembolic complications
  - Cost

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NovoSeven RT [package insert]. Novo Nordisk 2014
Characterization of In-hospital Use

- Retrospective database analysis (2000-2008)
- Off-Label Use
  - Accounted for 97% of doses
  - Increased by 143-fold
    - 2000 = 125 (CI, 0 to 543)
    - 2008 = 17,813 (14,381 to 22,240)
- Rapid expansion of use
  - Cardiovascular surgery
  - Trauma
- Academic vs. Non-Academic Institutions
  - Majority of use accounted for by non-academic hospitals
    - (68% [CI, 39 to 97%])

Factor Stewardship Programs

- Pharmacist-directed blood factor stewardship program
  - **Target:**
    - Off-label utilization of rFVIIa and PCC
    - Limit use to established organization guidelines
  - **Strategies:**
    - Development of institutional guidelines (cardiac surgery)
    - Dose limitations based on current available evidence
    - Continuous infusions of factors for hemophilia patients
  - **Findings:**
    - Reduction in the number of blood factor doses despite increases in the volume of patients treated
    - Annual cost savings $375,000 (rFVIIa) - $4,000,000 (comprehensive program)
Dosing Guideline for 4-Factor Prothrombin Complex Concentrate (Kcentra®) in Cardiac Surgery Patients for Pharmacists

BACKGROUND:

- Limited evidence for non-anticoagulation reversal use of 4-Factor PCC (Kcentra®) in cardiac surgery patients with refractory bleeding. Primary literature and current outside hospital practices suggest dosing of 500-1500 units or 10-25 units/kg

ALGORITHM:

- Kcentra® may be administered to cardiac surgery patients if the transfusion algorithm for the management of massive refractory blood loss has failed to control severe bleeding (e.g. patient failed cryoprecipitate and platelets). No hematology consult required for this indication

DOSING:

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>IV Dose</th>
</tr>
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<tbody>
<tr>
<td>&lt; 100 kg</td>
<td>1000 units</td>
</tr>
<tr>
<td>≥ 100 kg</td>
<td>1500 units</td>
</tr>
</tbody>
</table>

- If bleeding remains uncontrolled with one dose of Kcentra®, may consider repeating same dose
- Patients with prior anticoagulation exposure may require higher dosing than above per provider
Patient-Specific Considerations

• Assess for each patient:
  ▪ Acid-Base Status
    o rFVIIa activity decreases by 90% at pH 7.0
  ▪ Body Temperature
    o rFVIIa activity maintained at 33°C
    o Other coagulation proteases are impaired
  ▪ Co-Factors
    o Calcium, fibrinogen, platelets
  ▪ Timing
    o Short half-life (2 hours)
  ▪ Risk of Thromboembolic Events
    o Vascular grafts, prosthetic heart valves, malignancy, sepsis, DIC, ECMO, LVADs
    o History venous or arterial thromboembolic events

Thromboembolic Events

- Pooled analysis of 35 RCTs
  - Thromboembolic rates comparing rFVIIa to placebo

Findings:

<table>
<thead>
<tr>
<th>Arterial Thromboembolic Events</th>
<th>rFVIIa</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 yr</td>
<td>1/70 (1.4)</td>
<td>1/51 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-64 yr</td>
<td>73/1764 (4.1)</td>
<td>34/1107 (3.1)</td>
<td>1.36 (0.89-2.08)</td>
<td>0.15</td>
</tr>
<tr>
<td>65-75 yr</td>
<td>33/427 (7.7)</td>
<td>8/225 (3.6)</td>
<td>2.12 (0.95-4.71)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥ 75 yr</td>
<td>34/315 (10.8)</td>
<td>6/147 (4.1)</td>
<td>3.02 (1.22-7.48)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusion:

- Significant increase in risk of arterial thromboembolic events with off-label rFVIIa use
- No difference in venous thromboembolic events
- Highest risk amongst elderly patients (≥ 75 yr)
Dosing Considerations

• Off-Label Use
  ▪ Optimal dose unknown – lack of controlled studies
  ▪ Wide variations in clinical practice

• Lab Monitoring
  ▪ Lack of validated modalities to measure fVIIa activity
  ▪ Reliance on subjective assessment of hemostasis of patient

• Efficacy
  ▪ In-hospital, off-label use does not reduce mortality for ICH, cardiac surgery or body trauma

• Dosing
  ▪ Range 10-90 mcg/kg (consider 30 mcg/kg to start)
  ▪ Round to nearest vial size
  ▪ Multiple doses?

rFVIIa Summary

• Life threatening bleed
  • Inadequate response to conventional therapy
  • Appropriate blood products have been administered or unable to receive/tolerate blood products
  • Consider impact of acidosis and hypothermia
  • Variety of dosing strategies
  • No laboratory test to assess effectiveness
Additional Agents

• Many more!
  ▪ Desmopressin
  ▪ Epoetin alfa
  ▪ Conjugated estrogens
  ▪ Vitamin K
  ▪ Aminocaproic acid
  ▪ Tranexamic acid (TXA)
  ▪ Local hemostatics (thrombin)
Conclusions

• Pharmacists can play a vital role in the resuscitation of a coagulopathic patient
  • Consider patient-specific factors to maximize coagulation
  • Maintain an awareness of the indications and side effect profile of blood products
  • Assist in the management of the secondary consequences of blood products
  • Recognize the benefits and limitations of available hemostatic agents
Acute Dysglycemia: Tricks and Traps

Rachelle Firestone, Pharm.D., BCPS
Critical Care Pharmacist
University of California, Davis Medical Center
I have no conflicts of interest to disclose.
Learning Objectives

1. Identify evidence-based glycemic targets in the critically ill
2. Develop a safe and effective plan for transitioning ICU patients from intravenous to subcutaneous insulin
3. Discuss techniques for the prevention of hypoglycemia
Outline

• Clinical evidence for glucose control in the ICU
• Intravenous insulin
• Transitioning from intravenous → subcutaneous insulin
• Preventing hypoglycemia
Dysglycemia in the Critically Ill

- Hyperglycemia occurs frequently in the ICU, both in patients with and without diabetes
- Associated with an increased risk for death and infection
- Contributing factors
  - Stress hormone release
  - Sepsis, surgical trauma
  - Renal failure
  - Catecholamine & steroid use
  - Dense caloric nutrition
  - Insulin titration errors

Diabetes Care. 2016;39(suppl 1):S1-S106
Hyperglycemia and Mortality

Mortality (%) vs. Mean Glucose Value (mg/dL)

- 80-99
- 100-119
- 120-139
- 140-159
- 160-179
- 180-199
- 200-249
- 250-299
- >300

Krinsley JS. Mayo Clin Proc. 2003;78:1471-1478. Adapted from AACE.
2001 – Leuven SICU Study

- 1,548 surgical ICU patients, receiving mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>Treatment Threshold (mg/dL)</th>
<th>Target Glucose Level (mg/dL)</th>
<th>Mean Daily Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy (n=783)</td>
<td>215</td>
<td>180-200</td>
<td>153</td>
</tr>
<tr>
<td>Intensive therapy (n=765)</td>
<td>110</td>
<td>80-110</td>
<td>103</td>
</tr>
</tbody>
</table>

2001 – Leuven SICU Study

Hospital Mortality
OR [95% CI]
0.64 [0.45, 0.91]
2006 – Leuven MICU Study

- 1,200 medical ICU patients

<table>
<thead>
<tr>
<th></th>
<th>Treatment Threshold (mg/dL)</th>
<th>Target Glucose Level (mg/dL)</th>
<th>Mean Daily Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>215</td>
<td>180-200</td>
<td>153</td>
</tr>
<tr>
<td>(n=605)</td>
<td></td>
<td></td>
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<tr>
<td>Intensive therapy</td>
<td>110</td>
<td>80-110</td>
<td>111</td>
</tr>
<tr>
<td>(n=595)</td>
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</tbody>
</table>

Hospital Mortality
OR [95% CI]
0.89 [0.71, 1.13]

- Mortality benefit seen in SICU study was not replicated here
2009 – NICE-SUGAR Study

- 6,104 medical and surgical ICU patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target Glucose Level (mg/dL)</th>
<th>Mean Daily Glucose (mg/dL)</th>
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<tbody>
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<td>145</td>
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<td>(n=3050)</td>
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<tr>
<td>Intensive therapy</td>
<td>81-108</td>
<td>118</td>
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<tr>
<td>(n=3054)</td>
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</table>
2009 – NICE-SUGAR Study

# 2009 – NICE-SUGAR Study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=3010)</th>
<th>Conventional Control (N=3012)</th>
<th>Odds Ratio for Death (95% CI)</th>
<th>P Value for Heterogeneity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no. of deaths/no. with data available</td>
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<td></td>
<td></td>
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<tr>
<td>Operative admission</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>272/1111</td>
<td>222/1121</td>
<td>1.31 (1.07–1.61)</td>
<td>0.10</td>
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<tr>
<td>No</td>
<td>557/1898</td>
<td>529/1891</td>
<td>1.07 (0.93–1.23)</td>
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<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Yes</td>
<td>195/615</td>
<td>165/596</td>
<td>1.21 (0.95–1.55)</td>
<td>0.60</td>
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<tr>
<td>No</td>
<td>634/2394</td>
<td>586/2416</td>
<td>1.12 (0.99–1.28)</td>
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<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>202/673</td>
<td>172/626</td>
<td>1.13 (0.89–1.44)</td>
<td>0.93</td>
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<td>No</td>
<td>627/2335</td>
<td>579/2386</td>
<td>1.15 (1.01–1.31)</td>
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<tr>
<td>Trauma</td>
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<td></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>41/421</td>
<td>57/465</td>
<td>0.77 (0.50–1.18)</td>
<td>0.07</td>
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<tr>
<td>No</td>
<td>788/2587</td>
<td>694/2547</td>
<td>1.17 (1.04–1.32)</td>
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<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥ 25</td>
<td>336/927</td>
<td>363/944</td>
<td>1.14 (0.95–1.37)</td>
<td>0.84</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>442/2080</td>
<td>387/2066</td>
<td>1.17 (1.01–1.36)</td>
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<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>134/392</td>
<td>140/378</td>
<td>0.88 (0.66–1.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>No</td>
<td>695/2616</td>
<td>611/2634</td>
<td>1.20 (1.06–1.36)</td>
<td></td>
</tr>
<tr>
<td>All deaths at day 90</td>
<td>829/3010</td>
<td>751/3012</td>
<td>1.14 (1.02–1.28)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

2009 – NICE-SUGAR Study

- 2012 follow-up publication showed excess mortality was due to moderate-severe hypoglycemia

- More pronounced in patients with distributive shock

- Severe hypoglycemia = BG ≤40 mg/dL

- 6.8% vs 0.5% (OR 14, 95% CI 9.0-25.9; P<0.001)
## Guidelines for Glucose Management in ICU

<table>
<thead>
<tr>
<th>Year</th>
<th>Organization</th>
<th>Patient Population</th>
<th>Treatment Threshold (mg/dL)</th>
<th>Target Glucose Level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>American Association of Clinical Endocrinologists &amp; American Diabetes Association</td>
<td>ICU</td>
<td>180</td>
<td>140-180</td>
</tr>
<tr>
<td>2011</td>
<td>Institute for Healthcare Improvement</td>
<td>ICU</td>
<td>Not stated</td>
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<tr>
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<td>Surviving Sepsis Campaign</td>
<td>ICU (severe sepsis)</td>
<td>180</td>
<td>≤180</td>
</tr>
<tr>
<td>2014</td>
<td>American College of Cardiology &amp; American Heart Association</td>
<td>ICU (ACS)</td>
<td>180</td>
<td>&lt;180</td>
</tr>
</tbody>
</table>

Current Glycemic Goals

- ADA recommendations for ICU patients with persistent hyperglycemia
  - Target BG 140-180 mg/dL

- Intravenous insulin is the best method for achieving glycemic targets

- Minimize hypoglycemia (BG < 70)
Clinical evidence for glucose control in the ICU

- Intravenous insulin
- Transitioning from intravenous → subcutaneous insulin
- Preventing hypoglycemia
Intravenous Insulin

- Intravenous insulin is preferred over subcutaneous injection.
- Allows for rapid dose adjustments based on glycemic fluctuations and insulin dose.
- Frequent monitoring required.
- Use a *validated* protocol to minimize hypoglycemia.
  - Many published options (Yale, UPMC).
  - Education and demonstrated competency.
Intravenous Insulin

• High alert, high risk medication!
  
  • TJC: 1 of the top 5 highest risk medications in the inpatient setting
  
  • Errors in ordering, dispensing, and administration → consequences can be catastrophic
  
  • Standardized concentration (1 unit/mL), standardized protocols with online calculators, smart pumps

Diabetes Care 2009 Jun; 32(6): 1119-1131
Clinical evidence for glucose control in the ICU

Intravenous insulin

• Transitioning from intravenous → subcutaneous insulin
• Preventing hypoglycemia
Who needs transitioning?

• Not all critically ill patients on low-dose insulin infusions will require transition to basal/short-acting regimen

  • Type 1 DM
  
  • Type 2 DM on insulin prior to admission

  • Type 2 DM or persistent acute hyperglycemia requiring ≥ 2 units/hour of insulin

• Other considerations: steroids, vasopressors, diet
How To Transition

• Ideally patient should be on stable infusion rate for 3-6h prior to transition

1. Calculate average insulin infusion rate during relatively steady-state period in last 6h
2. Multiple by 24h
3. If DM1, apply correction of 0.7 to TDDI. If DM2, apply correction of 0.8.
4. Divide TDDI → 50% basal coverage + 50% short-acting or rapid-acting
5. Discontinue insulin infusion 2h after basal coverage is given
Calculating SC insulin dose

Example: JM has received an average of 2 units/hour during previous 6h. She has a history of DM2 and is currently NPO.

1. Calculate average insulin infusion rate during relatively steady-state period in last 6h
   2 units/h
2. Multiple by 24h
   24h insulin requirement (TDDI) = 2 units/h x 24h = 48 units
3. If DM1, apply correction of 0.7 to TDDI. If DM2, apply correction of 0.8.
   48 units x 0.8 = 38 units
4. Divide TDDI $\rightarrow$ 50% basal coverage + 50% short-acting or rapid-acting
   38 units $\rightarrow$ **19 units basal + 19 units short acting (either 4-5 units q6h or 6 units with meals)**
5. Discontinue insulin infusion 2h after basal coverage is given
### Therapy Options

#### Enteral nutrition
1. Insulin infusion
2. Basal (once or twice daily) + correction
3. Basal + scheduled q6h + correction
   
   **Basal:** short-acting = TDDI 50:50%

#### Parenteral nutrition
1. Begin BG monitoring (can stop if BG <140 x 24-48 hours)
2. Low dose correction if **no** h/o DM
3. Increase TDDI by 20-40% if h/o DM

#### Steroids
1. Begin BG monitoring (can stop if BG <140 x 24-48 hours)
2. Low dose correction if **no** h/o DM
3. Increase TDDI by 20-40% if h/o DM

### Other Considerations

- ? Bolus versus continuous tube feeds
- ? Insulin in TPN bag + correction
- Use caution when tapering!
Clinical evidence for glucose control in the ICU

Intravenous insulin

Transitioning from intravenous → subcutaneous insulin

- Preventing hypoglycemia
A single episode of severe hypoglycemia (SH) is independently associated with a higher risk of mortality

- OR 3.233, 95% CI [2.251, 4.644]

Risk factors for SH, BG < 40

- Renal failure
- Interruption of nutrition without adjustment in insulin therapy
- Mechanical ventilation
- Sepsis + vasoactive infusions
- CRRT with bicarb-based replacement fluids
- Longer ICU stay
Preventing Hypoglycemia

• Recognize triggering events
  - Transportation (imaging, etc) causing meal delay
  - Interruption of IV dextrose, TPN, enteral feeds, CRRT
  - New NPO status

• Regular glucose monitoring, adjustment of insulin doses, and administration of carbohydrate source, IV dextrose, or glucagon as needed

• Improve communication/coordination between departments
Treating Hypoglycemia

• Implementing a clear hypoglycemia protocol is vital

• Nursing driven, treat without delay
  1. Stop insulin infusion
  2. Give oral dextrose (if patient able to tolerate)
  3. Give IV dextrose or glucagon → 10-20g of D50
  4. Repeat BG in 15 mins and re-treat as needed to achieve BG > 70
Outline

- Clinical evidence for glucose control in the ICU
- Intravenous insulin
- Transitioning from intravenous → subcutaneous insulin
- Preventing hypoglycemia
# Case Presentation

45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
<th>20:00</th>
<th>00:00</th>
<th>04:00</th>
<th>08:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>210</td>
<td>240</td>
<td>310</td>
<td>365</td>
</tr>
<tr>
<td>Insulin (units)</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Diet</td>
<td>NPO</td>
<td>NPO</td>
<td>NPO</td>
<td></td>
</tr>
</tbody>
</table>

- What is the underlying etiology of his acute dysglycemia?
- What is the best argument for urgent intervention?
45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
<th>20:00</th>
<th>00:00</th>
<th>04:00</th>
<th>08:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>210</td>
<td>240</td>
<td>310</td>
<td>365</td>
</tr>
<tr>
<td>Insulin (units/hr)</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>NPO</td>
<td>NPO</td>
<td>NPO</td>
<td></td>
</tr>
</tbody>
</table>

- What mode of insulin therapy would you recommend and why?
- What is the target BG range?
Case Presentation

45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
<th>09:00</th>
<th>10:00</th>
<th>11:00</th>
<th>12:00</th>
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</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>245</td>
<td>255</td>
<td>265</td>
<td>55</td>
</tr>
<tr>
<td>Insulin (units/hr)</td>
<td>10</td>
<td>15</td>
<td>22.5</td>
<td>HELD</td>
</tr>
<tr>
<td>Diet</td>
<td>NPO</td>
<td></td>
<td>NPO</td>
<td></td>
</tr>
</tbody>
</table>

• What urgent therapy should be administered?
• How could you mitigate further risk of hypoglycemia?
Case Presentation – Day 3

45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
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<th>05:00</th>
<th>06:00</th>
<th>07:00</th>
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<tbody>
<tr>
<td><strong>Blood glucose (mg/dL)</strong></td>
<td>90</td>
<td>153</td>
<td>160</td>
<td>122</td>
</tr>
<tr>
<td><strong>Insulin (units/hr)</strong></td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>TFs @ goal</td>
<td>TFs @ goal</td>
<td>TFs @ goal</td>
<td></td>
</tr>
</tbody>
</table>

- When is it appropriate to transition from IV to SC insulin?
- What dose of basal insulin would you recommend?
Case Presentation – Day 7

45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
<th>07:00</th>
<th>09:00</th>
<th>11:00</th>
<th>13:00</th>
<th>15:00</th>
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</thead>
<tbody>
<tr>
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<td>120</td>
<td>180</td>
<td>69</td>
<td>205</td>
<td>80</td>
</tr>
<tr>
<td>Insulin (units/hr)</td>
<td>2</td>
<td>4</td>
<td>HELD</td>
<td>3</td>
<td>HELD</td>
</tr>
<tr>
<td>Diet</td>
<td>100% regular</td>
<td></td>
<td></td>
<td>100% regular</td>
<td></td>
</tr>
</tbody>
</table>

• What is driving his severe glycemic variability?
Diet + Insulin Infusion

Blood Glucose (mg/dL)

Insulin Infusion (units/hour)

Time (hours)

07:00  12:00  17:00
### Case Presentation – Day 10

45M with PMH of HTN, uncontrolled DM2 admitted for thermal injury (butane explosion), estimated 45% TBSA burns.

<table>
<thead>
<tr>
<th>Time</th>
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<th>03:00</th>
<th>09:00</th>
<th>15:00</th>
<th>21:00</th>
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</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>175</td>
<td>165</td>
<td>155</td>
<td>51</td>
<td>80</td>
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<tr>
<td>Insulin glargine (units)</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td>???</td>
</tr>
<tr>
<td>Insulin aspart (units)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>100% regular</td>
<td>Held for OR</td>
<td></td>
<td>D10W</td>
<td></td>
</tr>
</tbody>
</table>

- What triggering event led to the hypoglycemic episode?
- What would you do with the 21:00 glargine dose?
Additional Traps

• Continuous tube feeds + rapid-acting insulin

• Transition from tube feeds → regular diet with poor intake

• Insulin infusions without dextrose source
  • No safety net
Test Questions

1. A new medical ICU patient is admitted, and you see their most recent point-of-care BG measurement is 238. Which of the following is the most appropriate next step?
   a. Review medication list to see if you can avoid or minimize dextrose-containing fluids
   b. Ask physician to order a HgbA1c
   c. Recommend initiating insulin infusion
   d. Recommend restarting home metformin and glyburide

2. Which of the following is not a risk factor for severe hypoglycemia?
   a. History of sudden cardiac death
   b. Septic shock
   c. Mechanical ventilation
   d. Insulin therapy
To claim CPE credit, go to the CPE pages of your program book and:

1. Write down the course code given by the moderator;

2. Read the instructions for claiming credit online and note the last day to claim credit.
Opioid-sparing Analgesia in the ICU: Special Tools and Tactics

*Jeremiah J. Duby, PharmD, BCPS*
Clinical Pharmacy Specialist, Critical Care
Critical Care Residency Program Director
UC Davis Medical Center

Associate Clinical Professor
Touro University, College of Pharmacy
UCSF, School of Pharmacy
UC Davis, College of Medicine
Disclaimer(s)

- **industry ties:**
  - N/A

- **off-label medication use:**
  - N/A

- **product promotion:**
  - N/A

- **other financial interest(s):**
  - N/A

- **perspective:**
  - ICU pharmacist, academic medical center
Affiliations

- **University of California, Davis**
  - Critical Care Pharmacist (UCDMC)
  - Critical Care Residency Program Director
  - Assistant Clinical Professor of Medicine

- **Touro University, College of Pharmacy**
  - Associate Professor, Clinical Practice

- **U.C. San Francisco, College of Pharmacy**
  - Associate Professor, Pharmacy Practice
Learning Objectives

- describe evidence to support opioid-sparing effect of APAP, NSAIDs, ketamine, and gabapentin

- discuss advantages, disadvantages, and role of non-opioid agents
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

*Answer:* We recommend that IV opioids be considered as the first-line drug class of choice to treat non-neuropathic pain in critically ill patients (+1C). All available IV opioids, when titrated to similar pain intensity endpoints, are equally effective (C). We recommend that either enterally administered gabapentin or carbamazepine, in addition to IV opioids, be considered for the treatment of neuropathic pain (+1A). We suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (+2C).
Disadvantages of Opioid Therapy

- **Advantages**
  - Effective
  - Fast onset
  - Rapidly titratable

- **Disadvantages**
  - Side effects
    - Hypotension
    - Sedation
    - Respiratory depression
    - Constipation & ileus
    - Drag
    - Delay discharge
    - Opioid dependence

- **Side effects**
  - Hypotension
  - Sedation
  - Respiratory depression
  - Constipation & ileus
  - Drag
  - Delay discharge
  - Opioid dependence
“Non-Opioid Analgesics”

- APAP
- NSAIDs
- ketamine
- gabapentin, pregabalin
- lidocaine
What is the opioid-sparing effect of APAP in critically ill patients?
Opioid-sparing Effect of APAP (ICU)

- meta-analysis
  - none

- randomized controlled trials
  - none

- cohort studies
  - none

- other
  - post-operative pain studies
Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain (Review)

McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R

### IV APAP x 1: Effect on Post-Op Pain

- **36%** pts experienced 50% or greater pain relief with APAP
  - 16% with PBO
  - NNT = 5 for 50% reduction in pain
- **1.4 mg** (95% CI 1.0 – 1.8) reduction in morphine use


#### Analysis Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Para-propacetamol</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.1.1 Paracetamol vs placebo</td>
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<td></td>
<td></td>
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<tr>
<td>Jahr 2012 Study 3, 65+</td>
<td>5</td>
<td>15</td>
<td>4</td>
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<td>Juhl 2006</td>
<td>43</td>
<td>132</td>
<td>1</td>
</tr>
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<td>Koppert 2006</td>
<td>5</td>
<td>25</td>
<td>2</td>
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<tr>
<td>Moller 2005a</td>
<td>16</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>Sinatra 2005</td>
<td>15</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>272</strong></td>
<td><strong>121</strong></td>
<td><strong>13.0%</strong></td>
</tr>
</tbody>
</table>

Total events 84

Heterogeneity: Chi² = 10.56, df = 4 (P = 0.03); I² = 62%

Test for overall effect: Z = 4.18 (P < 0.0001)
30% pts experienced 50% or greater pain relief with APAP

- 10% with PBO
- NNT = 5 for 50% reduction in pain

1.9 mg (95% CI 1.4 – 2.4) reduction in morphine use

IV APAP ($$$)

Price Spikes
After some deals buying drugs from other companies, drug makers have hiked the prices significantly. Average wholesale prices:

- **NITROPRESS** ($1,500)
  (Treats high blood pressure)

- **OFIRMEV** ($1,020 for 24 vials)
  (Pain)

- **ISUPREL** ($1,347 per vial)
  (Heart problems)

- **VIMOVO** ($1,678 per 60 tablets)
  (Pain)

Source: Truven Health Analytics

$23 - 33/dose*

---

APAP

liquid, tablet, suppository

IV
APAP PK: IV vs PO vs PR

Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters After Single-Dose Administration of Intravenous, Oral, or Rectal Acetaminophen

Neil K. Singla, MD*;†; Cherri Parulan, BSN, RN*; Roselle Samson, CLS*; Joel Hutchinson, MD†; Rick Bushnell, MD†; Evelyn G. Beja, CRC*; Robert Ang, MD†; Mike A. Royal, MD, JD, MBA†

Disclosures: Neil K. Singla: Speaker Bureau, Research Support, Consultant; Cherri Parulan and Roselle Samson: Research Support; Joel Hutchinson, Rick Bushnell and Evelyn G. Beja: No conflicts to report; Robert Ang and Mike A. Royal: Shareholder and employee of Cadence Pharmaceuticals, Inc. Institutional Review Board that approved the study: Aspire IRB, 9340 Fuerte Dr, Suite 210, La Mesa, CA 91941, U.S.A.
PK: [Plasma]

Graph showing the mean acetaminophen plasma concentration (µg/mL) over time (hours) for different administration methods:

- IV acetaminophen 1000 mg
- Oral acetaminophen 1000 mg
- Rectal acetaminophen 1000 mg

The graph indicates a rapid rise and decline in concentration for IV administration, a slower rise and more sustained level for oral administration, and a slower rise and lower peak for rectal administration.
PK: [CSF]
Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making

Farah Jibril, Sherif Sharaby, Ahmed Mohamed, and Kyle J Wilby

Farah Jibril, BSc(Pharm), PharmD, is a Clinical Pharmacist at the National Center for Cancer Care and Research, Doha, Qatar.

Sherif Sharaby, BSc(Pharm), is a Pharmacist with the San Joaquin Valley Rehabilitation Hospital, Fresno, California.

Ahmed Mohamed, BSc(Pharm), PhD, is an Assistant Professor with the College of Pharmacy, Qatar University, Doha, Qatar.

Kyle J Wilby, BSP, ACPR, PharmD, is an Assistant Professor – Clinical Pharmacy and Practice, College of Pharmacy, Qatar University, Doha, Qatar.

Competing interests: None declared.
Total of 1703 potentially relevant trials identified through search of EMBASE (1148), IPA (112), Pubmed (443)

Dduplication excluded (N= 112)

Excluded based on title (N= 1533) and abstract (46)
  - Unrelated to the PICO question
    - Drug-Drug interaction
    - Pathophysiology/ pharmacology studies
  - Didn't meet inclusion criteria
    - Compared IV acetaminophen with other analgesics
    - Compared drugs other than acetaminophen
    - Combination with other drugs
    - No comparison
    - Non-randomized
    - Other dosage forms/formulations
    - Animal studies

After screening by abstract (N= 12)
Systematic Review

After screening by abstract (N= 12)

Excluded based on full-text review (N= 6)
  Did't meet inclusion criteria
  • Included acetaminophen prodrug (3)
  • Non-randomized (2)
  • Other indications (e.g. fever) (1)

6 RCTs included in systematic review

PK and PD

- **enteral**
  - high bioavailability: 13 – 21% of drug lost in absorption
    - 1-g dose PO: 89% absorption

- **IV**
  - ↑ Cmax
  - ↑ proportion of patients achieve *proposed* target levels

- ↑ levels → ↑ analgesic effect (?)
  - no established dose-response relationship
  - ↑ [APAP\textsubscript{plasma}] ≠ ↑ analgesic effect
Authors’ Conclusions

A major finding of this review was the absence of strong evidence suggesting superiority of IV acetaminophen administration over oral routes. Significant end points in the Pettersson and Brett trials for efficacy are called into question on the basis of clinical relevance and study design.\textsuperscript{22,24} For example, the significantly lower use of rescue opioids (ketobemidone) in the IV group in the study by Pettersson and others\textsuperscript{22} (17.4 mg versus 22.1 mg) is not clinically significant and would not justify preferentially giving postoperative IV therapy to patients who have undergone coronary artery bypass grafting. Similarly, the
Although no differences were found between groups of identified studies in terms of pain reduction, the results must be interpreted cautiously, as small sample sizes precluded testing for superiority. It was noted, however, that IV acetaminophen may be useful for opioid-sparing in postoperative pain. To date, no strong evidence exists that IV acetaminophen should replace any form of standard care. At most, the evidence indicates that this formulation could function as an adjunctive agent in patients unable to take oral forms.
What is the role of APAP in critically ill patients?
APAP: Role

- minimal risk of toxicity
  - with reasonable dosing and monitoring

- nominal major DDI
  - isoniazid, pneumococcal vaccine (PCV13), imatinib

- likely requires scheduled dosing for opioid-sparing effect

- IV APAP
  - patients that are strictly NPO (e.g. GI surgery)
What is the opioid-sparing effect of ketamine in critically ill patients?
Opioid-sparing Effect of Ketamine (ICU)

- meta-analysis
  - none

- randomized controlled trials
  - none

- cohort studies
  - none

- other
  - post-operative pain studies
Ketamine: Pharmacology

- phencyclidine derivative

- non-competitive NMDA receptor antagonist
  - binding sites in brain, spine, peripheral nerves

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipophillic: $V_D = 2.4 , \text{L/kg}$</td>
<td>rapid on/off &amp; short duration with initial doses</td>
</tr>
<tr>
<td>- rapid distribution ($t_{\frac{1}{2},\alpha} = 11 – 16 , \text{min}$)</td>
<td>- requires serial boluses or continuous infusion</td>
</tr>
<tr>
<td>hepatic metabolism (CYP3A4, CYP2D6, CYP2C9)</td>
<td>potential, pharmacokinetic DDI</td>
</tr>
<tr>
<td>- $t_{\frac{1}{2},\beta} = 2 – 3 , \text{hours}$</td>
<td>- titration similar to HM &amp; M</td>
</tr>
<tr>
<td>norketamine (active) eliminated in urine</td>
<td>potential for bioaccumulation in renal failure</td>
</tr>
<tr>
<td></td>
<td>- nominal with low dose over 72 hours</td>
</tr>
</tbody>
</table>
Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials

Li Wang, PhD · Bradley Johnston, PhD · Alka Kaushal, MBBS · Davy Cheng, MD · Fang Zhu, PhD · Janet Martin, PharmD

Conflicts of interest None declared.

Funding We thank the AMOSO Innovation Fund (Project #INN 11-008, Dr. J. Martin and Dr. D. Cheng) and the National Natural Science Foundation of China (Project # 71073105, Dr. L. Wang). The funding organizations had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data, or the preparation, review, or approval of the manuscript.
Post-operative Pain: PCA +/- Ketamine Infusion

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Time point</th>
<th>No. of comparisons</th>
<th>Sample size</th>
<th>Heterogeneity P value</th>
<th>$I^2$ (%)</th>
<th>WMD (95% CI)</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Pain score at rest</td>
<td>4-6 hr</td>
<td>25</td>
<td>1,406</td>
<td>&lt;0.001</td>
<td>87</td>
<td>-0.9 (-1.2 to -0.5)</td>
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<td>12 hr</td>
<td>20</td>
<td>1,093</td>
<td>&lt;0.001</td>
<td>89</td>
<td>-0.8 (-1.2 to -0.4)</td>
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<td>&lt;0.001</td>
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<td>-0.6 (-0.8 to -0.3)</td>
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<td>24</td>
<td>1,746</td>
<td>&lt;0.001</td>
<td>85</td>
<td>-0.4 (-0.6 to -0.2)</td>
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<tr>
<td></td>
<td>72 hr</td>
<td>4</td>
<td>215</td>
<td>&lt;0.001</td>
<td>89</td>
<td>-1.3 (-2.4 to -0.2)</td>
<td>-</td>
</tr>
<tr>
<td>Pain score during mobilization</td>
<td>4-6 hr</td>
<td>7</td>
<td>750</td>
<td>&lt;0.001</td>
<td>89</td>
<td>-0.1 (-0.9 to +0.7)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>12 hr</td>
<td>9</td>
<td>824</td>
<td>0.08</td>
<td>43</td>
<td>-0.5 (-0.8 to -0.2)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>24 hr</td>
<td>15</td>
<td>1,144</td>
<td>0.18</td>
<td>25</td>
<td>-0.4 (-0.6 to -0.2)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>48 hr</td>
<td>12</td>
<td>1,055</td>
<td>0.07</td>
<td>41</td>
<td>-0.5 (-0.8 to -0.2)</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative morphine consumption</td>
<td>24 hr</td>
<td>30</td>
<td>1,882</td>
<td>&lt;0.001</td>
<td>82</td>
<td>-5.0 (-7.2 to -2.8)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>48 hr</td>
<td>22</td>
<td>1,196</td>
<td>&lt;0.001</td>
<td>83</td>
<td>-12.7 (-18.9 to -6.6)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>72 hr</td>
<td>5</td>
<td>533</td>
<td>0.791</td>
<td>0</td>
<td>-20.2 (-27.7 to -12.7)</td>
<td>-</td>
</tr>
<tr>
<td>Patient satisfaction scores</td>
<td>24 hr</td>
<td>6</td>
<td>353</td>
<td>0.02</td>
<td>61</td>
<td>0.05 (-0.5 to 0.6)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>48 hr</td>
<td>4</td>
<td>217</td>
<td>0.03</td>
<td>67</td>
<td>0.02 (-1.1 to 1.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

# Post-operative Pain: PCA + Low-dose Ketamine

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Time point</th>
<th>No. of comparisons</th>
<th>Sample size</th>
<th>Heterogeneity P</th>
<th>I² (%)</th>
<th>WMD (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>30</td>
<td>2,143</td>
<td>0.03</td>
<td>35</td>
<td>-</td>
<td>0.71 (0.60 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>22</td>
<td>1,488</td>
<td>0.88</td>
<td>0</td>
<td>-</td>
<td>1.27 (0.81 to 1.98)</td>
<td></td>
</tr>
<tr>
<td>Vivid dreams</td>
<td>14</td>
<td>734</td>
<td>0.96</td>
<td>0</td>
<td>-</td>
<td>1.21 (0.77 to 1.90)</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>15</td>
<td>882</td>
<td>0.56</td>
<td>0</td>
<td>-</td>
<td>1.00 (0.55 to 1.84)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>15</td>
<td>1,287</td>
<td>0.41</td>
<td>3</td>
<td>-</td>
<td>0.92 (0.69 to 1.22)</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>12</td>
<td>1,030</td>
<td>0.06</td>
<td>45</td>
<td>-</td>
<td>0.59 (0.30 to 1.17)</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>8</td>
<td>549</td>
<td>0.86</td>
<td>0</td>
<td>-</td>
<td>0.76 (0.53 to 1.09)</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>3</td>
<td>260</td>
<td>0.69</td>
<td>0</td>
<td>-</td>
<td>1.53 (0.59, 3.96)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular adverse effects#</td>
<td>2</td>
<td>120</td>
<td>0.20</td>
<td>39</td>
<td>-</td>
<td>1.51 (0.14, 16.28)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Comparisons

The Effects of Small-Dose Ketamine on Morphine Consumption in Surgical Intensive Care Unit Patients After Major Abdominal Surgery

Nicolas Guillou, MD*, Michèle Tanguy, MD*, Philippe Seguin, MD*, Bernard Branger, MD‡, Jean-Pierre Campion, MD‡, and Yannick Mallédant, MD*

Financial Disclosures:
• not published
• not available via openpaymentsdata.cms.gov
### Clinical Comparison

<table>
<thead>
<tr>
<th>objective</th>
<th>“to determine whether the addition of small-dose ketamine could reduce the consumption of morphine and create fewer adverse effects in patients treated in the SICU”</th>
</tr>
</thead>
<tbody>
<tr>
<td>design</td>
<td>• prospective, randomized, double-blind</td>
</tr>
<tr>
<td>population</td>
<td>• major abdominal surgery</td>
</tr>
</tbody>
</table>
| intervention| • ketamine bolus 0.5 mg/kg IV x 1  
• 2 mcg/kg/min x 24 hrs, then 1 mcg/kg/min from 24 – 48 hrs |
| endpoint(s)| • pain score (VAS, 100-mm)  
• cumulative morphine PCA use (mg)                                                                                                                                                        |
### Clinical Comparison

**Table 1.** Demographic Data, Type of Surgery Performed, Intraoperative Dose of Sufentanil, and Severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine group</th>
<th>Morphine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 41 )</td>
<td>( n = 52 )</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>60 ± 16</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>Male/female (( n ))</td>
<td>27/14</td>
<td>41/11</td>
</tr>
<tr>
<td>Type of surgery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatectomy</td>
<td>54</td>
<td>44</td>
</tr>
<tr>
<td>Esophageal surgery</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Others</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Intraoperative sufentanil dose (( \mu g ))*</td>
<td>149 ± 64</td>
<td>144 ± 58</td>
</tr>
<tr>
<td>SAPS II*</td>
<td>30 ± 7</td>
<td>31 ± 8</td>
</tr>
</tbody>
</table>
Visual analog scale scores (mm)

0  10  20  30  40  50  60  70

Effect on Pain Scores

Hours after admission in the ICU

What are the advantages, disadvantages, and role of ketamine in critically ill patients?
## Ketamine

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ psychomimetic effects:</td>
<td>➢ low-dose ketamine (LDK)</td>
</tr>
<tr>
<td>▪ hallucinations, dysphoria</td>
<td>▪ low risk of psychomimetic effects</td>
</tr>
<tr>
<td>▪ low-dose ketamine (LDK)</td>
<td>▪ midazolam or lorazepam</td>
</tr>
<tr>
<td>➢ sedation</td>
<td>▪ minimal sedative effect</td>
</tr>
<tr>
<td>➢ sympathomimetic effects (↑ BP)</td>
<td>▪ no appreciable cardiovascular effects</td>
</tr>
<tr>
<td>➢ salivary and respiratory secretions</td>
<td>➢ anti-sialagogue</td>
</tr>
<tr>
<td>➢ ↑ intra-ocular and intracranial pressure (?)</td>
<td>➢ relative contraindications</td>
</tr>
<tr>
<td>➢ ↓ seizure threshold (?)</td>
<td>▪ intracranial hypertension (e.g. TBI)</td>
</tr>
<tr>
<td></td>
<td>▪ h/o seizure, recent intracranial injury</td>
</tr>
</tbody>
</table>
# Low-dose Ketamine (LDK)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ dose-dependent effect:</td>
<td>➢ IV bolus:</td>
</tr>
<tr>
<td>▪ analgesia → dissociative sedation → anesthesia</td>
<td>▪ 0.1 – 0.3 mg/kg every 10 – 15 min</td>
</tr>
<tr>
<td>➢ multiple routes of administration</td>
<td>➢ IV infusion:</td>
</tr>
<tr>
<td></td>
<td>▪ 1 – 5 mcg/kg/min (50 – 300 mcg/k/hr)</td>
</tr>
<tr>
<td>➢ no cardiovascular suppression</td>
<td>➢ PO</td>
</tr>
<tr>
<td></td>
<td>▪ ???</td>
</tr>
<tr>
<td>➢ inexpensive</td>
<td>➢ may be used in patients with tenuous hemodynamics</td>
</tr>
<tr>
<td></td>
<td>➢ no financial barriers</td>
</tr>
</tbody>
</table>
Low-Dose Ketamine (LDK): Potential Role

- severe pain & high opioid requirements
- acute pain
  - peri-operative period
  - trauma
  - burn
- adjuvant to opioid therapy for short-term use
  - tachyphylaxis likely develops (hours to days)
What is the opioid-sparing effect of NSAIDs in critically ill patients?
Opioid-sparing Effect of NSAIDs (ICU)

- meta-analysis
  - none

- randomized controlled trials
  - none

- cohort studies
  - none

- other
  - post-operative pain studies
NSAIDs: Opioid-sparing Effect (Post-op)

Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review

E. Maund*, C. McDaid, S. Rice, K. Wright, B. Jenkins and N. Woolacott

Objective: “to determine explicitly which class, if any, of non-opioid analgesic (paracetamol, NSAIDs, or COX-2 inhibitor) is most effective at reducing morphine consumption and morphine-related adverse effects when used as part of multimodal analgesia after major surgery”

Conflict of interest
None declared.
NSAIDs: Opioid-sparing Effect (Post-op)

References identified from the search strategies: n=4357

Excluded on the basis of reviewing title and abstract: n=4210

References of trials included in Elia and colleagues: n=52

Papers ordered for more detailed evaluation: n=199

Papers excluded: n=139

Included trials: n=60

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Morphine consumption, unadjusted, mean difference, mg (95% CrI)</th>
<th>Morphine consumption, adjusted, mean difference, mg (95% CrI)</th>
<th>Nausea and PONV, pairwise OR (95% CrI)</th>
<th>Sedation, pairwise OR (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol vs placebo</td>
<td>$-6.34 \left( -9.02, -3.65 \right)$</td>
<td>$-8.68 \left( -11.43, -5.94 \right)$</td>
<td>1.00 (0.60, 1.53)</td>
<td>1.62 (0.32, 5.02)</td>
</tr>
<tr>
<td>NSAID vs placebo</td>
<td>$-10.18 \left( -11.65, -8.72 \right)$</td>
<td>$-9.45 \left( -10.90, -8.01 \right)$</td>
<td>0.70 (0.53, 0.88)</td>
<td>0.53 (0.20, 1.01)</td>
</tr>
<tr>
<td>COX-2 vs placebo</td>
<td>$-10.92 \left( -12.77, -9.08 \right)$</td>
<td>$-10.67 \left( -12.42, -8.94 \right)$</td>
<td>0.88 (0.61, 1.25)</td>
<td>0.63 (0.18, 1.49)</td>
</tr>
<tr>
<td>NSAID vs paracetamol</td>
<td>$-3.85 \left( -6.80, -0.89 \right)$</td>
<td>$-0.77 \left( -3.75, 2.21 \right)$</td>
<td>0.74 (0.44, 1.17)</td>
<td>0.51 (0.08, 1.63)</td>
</tr>
<tr>
<td>COX-2 vs paracetamol</td>
<td>$-4.58 \left( -7.83, -1.35 \right)$</td>
<td>$-1.99 \left( -5.24, 1.24 \right)$</td>
<td>0.93 (0.51, 1.63)</td>
<td>0.63 (0.07, 2.33)</td>
</tr>
<tr>
<td>COX-2 vs NSAID</td>
<td>$-0.74 \left( -3.03, 1.56 \right)$</td>
<td>$-1.22 \left( -3.43, 1.00 \right)$</td>
<td>1.28 (0.81, 1.97)</td>
<td>1.40 (0.30, 4.31)</td>
</tr>
<tr>
<td>Number of arms; residual deviance</td>
<td>116; 186</td>
<td>116; 114</td>
<td>86; 97</td>
<td>31; 41</td>
</tr>
</tbody>
</table>

NSAIDs: Effect on [Normal] Renal Function

Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function (Review)

Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP

Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002765.
## NSAIDs: Effect on [Normal] Renal Function

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Change in creatinine clearance (mL/min) on Day 1</td>
<td>6</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Multiple NSAID doses versus placebo</td>
<td>3</td>
<td>66</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-24.63 [-42.29, -6.98]</td>
</tr>
<tr>
<td>1.2 Single NSAID dose versus placebo</td>
<td>3</td>
<td>75</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-10.40 [-25.65, 4.86]</td>
</tr>
<tr>
<td>2 Change in creatinine clearance (mL/min) on Day 2</td>
<td>4</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Multiple NSAID doses versus placebo</td>
<td>2</td>
<td>44</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-7.59 [-30.66, 15.47]</td>
</tr>
<tr>
<td>2.2 Single NSAID dose versus placebo</td>
<td>2</td>
<td>70</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.22 [-33.27, 35.72]</td>
</tr>
</tbody>
</table>

Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002765.
### NSAIDs: Effect on [Normal] Renal Function

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NSAID N</th>
<th>Mean(SD)</th>
<th>Placebo N</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>IV Random, 95% CI</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitken 1992</td>
<td>10</td>
<td>-24.1 (41.06)</td>
<td>15</td>
<td>-3.3 (40.71)</td>
<td></td>
<td></td>
<td>12.4%</td>
<td>-20.80 [-53.54, 11.94]</td>
</tr>
<tr>
<td>Power 1992</td>
<td>10</td>
<td>1 (37.32)</td>
<td>10</td>
<td>29 (38.11)</td>
<td></td>
<td></td>
<td>12.2%</td>
<td>-28.00 [-61.06, 5.06]</td>
</tr>
<tr>
<td>Irwin 1995</td>
<td>11</td>
<td>-6 (27.87)</td>
<td>10</td>
<td>19 (34.77)</td>
<td></td>
<td></td>
<td>18.1%</td>
<td>-25.00 [-52.12, 2.12]</td>
</tr>
<tr>
<td>Brinkmann 1998</td>
<td>13</td>
<td>3.6 (31.18)</td>
<td>13</td>
<td>17.8 (40.66)</td>
<td></td>
<td></td>
<td>17.2%</td>
<td>-14.20 [-42.05, 13.65]</td>
</tr>
<tr>
<td>Slaven 1998</td>
<td>10</td>
<td>-20.8 (27.86)</td>
<td>9</td>
<td>-9.3 (21.19)</td>
<td></td>
<td></td>
<td>27.2%</td>
<td>-11.50 [-33.63, 10.63]</td>
</tr>
<tr>
<td>Jones 2000</td>
<td>15</td>
<td>18 (32.14)</td>
<td>15</td>
<td>21 (54.84)</td>
<td></td>
<td></td>
<td>12.9%</td>
<td>-3.00 [-35.17, 29.17]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)** 69 72

Heterogeneity: Tau² = 0.0; Chi² = 1.81, df = 5 (P = 0.88); I² = 0.0%

Test for overall effect: Z = 2.80 (P = 0.0051)

2. Change in creatinine clearance on Day 2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NSAID N</th>
<th>Mean(SD)</th>
<th>Placebo N</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>IV Random, 95% CI</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitken 1992</td>
<td>10</td>
<td>13.6 (54.45)</td>
<td>15</td>
<td>6.8 (34.43)</td>
<td></td>
<td></td>
<td>14.1%</td>
<td>6.80 [-31.18, 44.78]</td>
</tr>
<tr>
<td>Power 1992</td>
<td>9</td>
<td>1 (33.6)</td>
<td>10</td>
<td>17 (30.64)</td>
<td></td>
<td></td>
<td>24.1%</td>
<td>-16.00 [-45.03, 13.03]</td>
</tr>
<tr>
<td>Jones 2000</td>
<td>15</td>
<td>29 (37.51)</td>
<td>15</td>
<td>6 (65.78)</td>
<td></td>
<td></td>
<td>13.8%</td>
<td>23.00 [-15.32, 61.32]</td>
</tr>
<tr>
<td>Khalil 2006</td>
<td>21</td>
<td>0 (29.2)</td>
<td>19</td>
<td>13 (36.4)</td>
<td></td>
<td></td>
<td>47.9%</td>
<td>-13.00 [-33.59, 7.59]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)** 55 59

100.0% -16.48 [-28.03, -4.94]

Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD002765.
Objective: “to estimate the association between NSAID use and accelerated CKD progression (estimated glomerular filtration rate decline ≥ 15ml/min”

Declaration

Funding: Wolfson Foundation; North Staffordshire Medical Institute.
Ethical approval: none.
Conflict of interest: none.
NSAIDs: Effect on Patients with CKD

**NSAIDs: Effect on Patients with CKD**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular Dose NSAID use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gooch</td>
<td>-0.1985</td>
<td>0.170257</td>
<td>12.7%</td>
<td>0.82 [0.59, 1.14]</td>
</tr>
<tr>
<td>Yarger</td>
<td>-0.0661</td>
<td>0.092097</td>
<td>25.0%</td>
<td>0.94 [0.78, 1.12]</td>
</tr>
<tr>
<td>Hemmelgarn</td>
<td>0</td>
<td>0.07339</td>
<td>29.3%</td>
<td>1.00 [0.87, 1.15]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>67.0%</td>
<td>0.96 [0.86, 1.07]</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 0.80 (P = 0.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **High Dose NSAID use** | | | | |
| Yarger             | 0.2437         | 0.210608 | 9.3%   | 1.28 [0.84, 1.93]           |
| Gooch             | 0.2311         | 0.098483 | 23.7%  | 1.26 [1.04, 1.53]           |
| **Subtotal (95% CI)** | | | 33.0%  | 1.26 [1.06, 1.50]           |
| **Heterogeneity:** Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0% | | | | |
| **Test for overall effect:** Z = 2.62 (P = 0.009) | | | | |

| **Total (95% CI)** | | | 100.0%  | 1.04 [0.90, 1.20] |
| **Heterogeneity:** Tau² = 0.01; Chi² = 8.26, df = 4 (P = 0.08); I² = 52% | | | | |
| **Test for overall effect:** Z = 0.49 (P = 0.63) | | | | |
| **Test for subgroup differences:** Chi² = 7.01, df = 1 (P = 0.008), I² = 85.7% | | | | |
NSAIDS: Vascular and GI Effects

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Coxib and traditional NSAID Trialists’ (CNT) Collaboration*

objective: “to characterise and quantify the cardiovascular and gastrointestinal risks of particular NSAID regimens among different types of patients, particularly those at increased risk of vascular disease”

Funding UK Medical Research Council and British Heart Foundation.

NSAIDS: Vascular and GI Effects

A

Coxib

Baseline major vascular event risk

- Fatal
- + Fatal+non-fatal

Baseline upper gastrointestinal complication risk

Absolute annual excess risk per 1000 (SE)

NSAIDS: Vascular and GI Effects

Diclofenac (75 mg twice a day)
NSAIDS: Vascular and GI Effects

C  Ibuprofen (800 mg three times a day)

Absolute annual excess risk per 1000 (SE)

9
3
2

15

6

NSAIDS: Vascular and GI Effects

D. Naproxen (500 mg twice a day)

Objective: “to examine whether the duration of NSAID treatment influenced the cardiovascular risk of NSAIDs in a population of patients after MI”
NSAID: Risk of Death

Risk of death associated with NSAID treatment

<table>
<thead>
<tr>
<th>NSAID</th>
<th>HR [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NSAIDs &gt; 90 days</td>
<td>1.34 [1.29-1.53]</td>
</tr>
<tr>
<td>Celecoxib &gt; 90 days</td>
<td>1.82 [1.61-2.05]</td>
</tr>
<tr>
<td>Ibuprofen &gt; 90 days</td>
<td>1.58 [1.44-1.74]</td>
</tr>
<tr>
<td>Diclofenac &gt; 90 days</td>
<td>1.86 [1.74-1.99]</td>
</tr>
<tr>
<td>Naproxen &gt; 90 days</td>
<td>1.56 [1.47-1.65]</td>
</tr>
<tr>
<td>0-7 days</td>
<td>1.10 [0.71-1.68]</td>
</tr>
<tr>
<td>7-14 days</td>
<td>1.14 [0.90-2.43]</td>
</tr>
<tr>
<td>14-30 days</td>
<td>1.39 [1.29-2.02]</td>
</tr>
<tr>
<td>30-90 days</td>
<td>2.33 [1.79-3.02]</td>
</tr>
<tr>
<td>0-7 days</td>
<td>1.74 [1.42-2.13]</td>
</tr>
<tr>
<td>7-14 days</td>
<td>1.71 [1.47-1.99]</td>
</tr>
<tr>
<td>14-30 days</td>
<td>0.92 [0.71-1.20]</td>
</tr>
<tr>
<td>30-90 days</td>
<td>1.57 [1.27-1.94]</td>
</tr>
<tr>
<td>0-7 days</td>
<td>1.43 [1.22-1.67]</td>
</tr>
<tr>
<td>7-14 days</td>
<td>1.91 [1.73-2.11]</td>
</tr>
<tr>
<td>14-30 days</td>
<td>1.52 [1.38-1.69]</td>
</tr>
<tr>
<td>30-90 days</td>
<td>3.52 [2.93-4.20]</td>
</tr>
<tr>
<td>Diclofenac &gt; 90 days</td>
<td>2.57 [2.03-3.24]</td>
</tr>
<tr>
<td>Naproxen &gt; 90 days</td>
<td>2.08 [1.71-2.53]</td>
</tr>
<tr>
<td>0-7 days</td>
<td>2.61 [2.25-3.02]</td>
</tr>
<tr>
<td>7-14 days</td>
<td>2.02 [1.73-2.36]</td>
</tr>
<tr>
<td>14-30 days</td>
<td>1.63 [0.88-3.03]</td>
</tr>
<tr>
<td>30-90 days</td>
<td>1.00 [0.63-1.68]</td>
</tr>
<tr>
<td>Naproxen &gt; 90 days</td>
<td>1.22 [0.71-2.10]</td>
</tr>
</tbody>
</table>
NSAID: Risk of Death & Recurrent MI

Risk of death/Re-MI associated with NSAID treatment

- **NSAID:**
  - Risk of Death & Recurrent MI

---

**HR(95% CI):**

- **All NSAIDs > 90 days:**
  - 1.45 [1.29-1.62]
  - 1.68 [1.50-1.88]
  - 1.45 [1.33-1.59]
  - 1.65 [1.55-1.75]
  - 1.55 [1.46-1.64]

- **Celecoxib > 90 days:**
  - 1.27 [0.87-1.85]
  - 1.38 [0.93-2.06]
  - 1.90 [1.46-2.48]
  - 1.62 [1.33-1.97]
  - 1.65 [1.42-1.92]

- **Ibuprofen > 90 days:**
  - 1.04 [0.83-1.30]
  - 1.50 [1.24-1.82]
  - 1.33 [1.15-1.53]
  - 1.70 [1.55-1.87]
  - 1.53 [1.40-1.69]

- **Diclofenac > 90 days:**
  - 3.26 [2.75-3.86]
  - 2.12 [1.69-2.67]
  - 1.67 [1.38-2.02]
  - 2.15 [1.86-2.48]
  - 1.92 [1.66-2.22]

- **Naproxen > 90 days:**
  - 1.76 [1.04-2.98]
  - 1.21 [0.63-2.32]
  - 1.20 [0.74-1.93]
  - 1.15 [0.80-1.65]
  - 1.50 [0.10-2.05]
High-Dose Ketorolac Affects Adult Spinal Fusion

A Meta-Analysis of the Effect of Perioperative Nonsteroidal Anti-Inflammatory Drugs on Spinal Fusion

Quan Li, MD,* Zhiyu Zhang, MD,† and Zhengdong Cai, MD‡

No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.
## NSAIDS vs Bone Healing

<table>
<thead>
<tr>
<th><strong>objective</strong></th>
<th>“to determine the effects of postoperative NSAIDs on spinal fusion”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>data source</strong></td>
<td>PubMed, EMBASE, OVID (1/68 to 12/08)</td>
</tr>
<tr>
<td><strong>study selection</strong></td>
<td>• comparative studies of inter-body vertebral fusion &amp; posterolateral inter-transverse fusion (PIF)</td>
</tr>
<tr>
<td><strong>review</strong></td>
<td>• 2 reviewers independently reviewed studies</td>
</tr>
</tbody>
</table>
NSAIDS vs Bone Healing

Studies identified from literature search and hand searches (n=558)

Studies excluded for reviews, letters, animal experiments, case reports (n=496)

Studies retrieved for more detailed evaluation (n=62)

Studies excluded (n=54)
  - Duplicate publication (n=12)
  - Without a control group (n=24)
    - Irrelevant trials (n=18)

Potentially eligible studies (n=8)

Studies excluded (n=3)
  - No detailed information about the dose of NSAIDs (n=1)
  - Participants including not only nonunion but also infection or other reasons for reoperation (n=1)
  - Article retracted by the journal (n=1)

Eligible studies (n=5)

# NSAIDS vs Bone Healing

## Data Investigated in the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>NSAIDs</th>
<th>Dose</th>
<th>Duration (d)</th>
<th>No. Patients</th>
<th>Control Group (No-NSAIDs)</th>
<th>Experiment Group (NSAIDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman</td>
<td>K</td>
<td>Normal</td>
<td>3</td>
<td>97</td>
<td>2/60</td>
<td>3/37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>3</td>
<td>191</td>
<td>3/61</td>
<td>26/130</td>
</tr>
<tr>
<td>Lumawig</td>
<td>DS</td>
<td>Normal</td>
<td>14</td>
<td>178</td>
<td>0/10</td>
<td>16/168</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>14</td>
<td>95</td>
<td>0/9</td>
<td>29/86</td>
</tr>
<tr>
<td>Park</td>
<td>K</td>
<td>Normal</td>
<td>3</td>
<td>88</td>
<td>2/58</td>
<td>5/30</td>
</tr>
<tr>
<td>Pradhan</td>
<td>K</td>
<td>High</td>
<td>2</td>
<td>320</td>
<td>4/92</td>
<td>12/228</td>
</tr>
<tr>
<td>Reuben</td>
<td>K</td>
<td>Normal</td>
<td>5</td>
<td>82</td>
<td>3/32</td>
<td>3/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>5</td>
<td>103</td>
<td>3/33</td>
<td>20/70</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td>Normal</td>
<td>5</td>
<td>156</td>
<td>3/32</td>
<td>9/124</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>Normal</td>
<td>5</td>
<td>93</td>
<td>2/33</td>
<td>5/60</td>
</tr>
</tbody>
</table>

K indicates ketorolac; DS, diclofenac sodium; R, rofecoxib; C, celecoxib; NSAIDs, nonsteroidal anti-inflammatory drugs.
NSAIDS (normal dose) vs Bone Healing

### 1.1.1 Normal Dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NSAIDs Events</th>
<th>NSAIDs Total</th>
<th>no NSAIDs Events</th>
<th>no NSAIDs Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman 1998(K, ND)</td>
<td>2</td>
<td>37</td>
<td>2</td>
<td>60</td>
<td>5.2%</td>
<td>1.62 [0.24, 11.02]</td>
</tr>
<tr>
<td>Lumawig 2009(DS, ND)</td>
<td>16</td>
<td>168</td>
<td>0</td>
<td>10</td>
<td>3.2%</td>
<td>2.15 [0.14, 33.49]</td>
</tr>
<tr>
<td>Park 2005(K, ND)</td>
<td>5</td>
<td>30</td>
<td>2</td>
<td>58</td>
<td>4.6%</td>
<td>4.83 [1.00, 23.45]</td>
</tr>
<tr>
<td>Reuben 2005(C, ND)</td>
<td>5</td>
<td>60</td>
<td>2</td>
<td>33</td>
<td>8.7%</td>
<td>1.38 [0.28, 6.70]</td>
</tr>
<tr>
<td>Reuben 2005(K, ND)</td>
<td>3</td>
<td>50</td>
<td>3</td>
<td>32</td>
<td>12.4%</td>
<td>0.64 [0.14, 2.98]</td>
</tr>
<tr>
<td>Reuben 2005(R, ND)</td>
<td>9</td>
<td>124</td>
<td>3</td>
<td>32</td>
<td>16.1%</td>
<td>0.77 [0.22, 2.70]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>469</td>
<td>225</td>
<td>50.1%</td>
<td></td>
<td></td>
<td>1.39 [0.74, 2.61]</td>
</tr>
</tbody>
</table>

Total events 40 12

Heterogeneity: Chi^2 = 4.34, df = 5 (P = 0.50); I^2 = 0%

Test for overall effect: Z = 1.03 (P = 0.30)

**Spine (Phila Pa 1976). 2011 Apr 1; 36(7): E461-8.**
**NSAIDS (high dose) vs Bone Healing**

### 1.1.2 High Dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Days</th>
<th>Events</th>
<th>Patients</th>
<th>Loss to follow-up</th>
<th>Total events</th>
<th>Heterogeneity: $\chi^2$, df = 3, $P$; $I^2$</th>
<th>Test for overall effect: $Z$, $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman 1998(K, HD)</td>
<td>26</td>
<td>130</td>
<td>61</td>
<td>3</td>
<td>87</td>
<td>$\chi^2 = 3.10$, df = 3, $P = 0.38$; $I^2 = 3%$</td>
<td>$Z = 3.29$, $P = 0.0010$</td>
</tr>
<tr>
<td>Lumawig 2009(DS, HD)</td>
<td>29</td>
<td>86</td>
<td>9</td>
<td>0</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pradhan 2008(K, HD)</td>
<td>12</td>
<td>228</td>
<td>92</td>
<td>4</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reuben 2005(K, HD)</td>
<td>20</td>
<td>70</td>
<td>33</td>
<td>3</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

- Total events: 983
- Heterogeneity: $\chi^2 = 9.64$, df = 9, $P = 0.38$; $I^2 = 7\%$
- Test for overall effect: $Z = 3.34$, $P = 0.0008$

**Spine (Phila Pa 1976). 2011 Apr 1; 36(7): E461-8.**

![Graph showing the comparison of experimental vs control groups]
Authors’ Conclusions

Key Points

- Short-time exposure to high-dose ketorolac showed a statistically significant adverse effect on adult spinal fusion.

- Short-time exposure to normal-dose NSAIDs, such as ketorolac, diclofenac sodium, celecoxib, or rofecoxib did not appear to produce inferior results than the no-NSAIDs group.

- Further study would be needed to determine whether long-time exposure to normal-dose NSAIDs could increase the risk of nonunion and whether certain types of NSAIDs would like to have worse effect on spinal fusion.
NSAIDs: Role

- comparable efficacy to APAP
  - unknown additive or synergistic effect
- substantial risk of major adverse effects
  - mitigated by dose and duration
- careful patient selection is key
Opioid-sparing Analgesia in the ICU:
Special Tools and Tactics

Jeremiah J. Duby, PharmD, BCPS
Critical Care Pharmacist, Specialist
Critical Care Residency Program Director
UC Davis Medical Center

Associate Clinical Professor
Touro University, College of Pharmacy
UCSF, School of Pharmacy
UC Davis, College of Medicine
To claim CPE credit, go to the CPE pages of your program book and:

1. Write down the course code given by the moderator;

2. Read the instructions for claiming credit online and note the last day to claim credit.
Learning Objectives

- Describe unique pharmacologic challenges in traumatic brain injury

- Discuss when, why, and how to initiate prophylaxis for posttraumatic seizures (PTS) and deep vein thrombosis (DVT)
Disclosure

I have no conflicts of interest to disclose.
Overview

Part I
  ◦ Traumatic brain injury review

Part II
  ◦ Posttraumatic seizure prophylaxis

Part III
  ◦ Venous thromboembolism (VTE) prophylaxis
Blunt or penetrating trauma to the brain

Common causes
- Falls, motor vehicle-related injuries, assault (i.e. firearms)

TBI Classification based on Glasgow Coma Scale (GCS) score:
- Mild – GCS 14-15
- Moderate – GCS 9-13
- Severe – GCS ≤ 8

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening response</td>
<td>Spontaneously</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Best verbal response</td>
<td>Oriented to time, place, person</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Best motor response</td>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Moves to localized pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Flexion withdrawal from pain</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Abnormal flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Abnormal extension</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

Total Score
- Best response: 15
- Comatose: ≤ 8
- Totally unresponsive: 3
Neurologic Damage

Primary insult (nonmodifiable)
- Edema
- Ischemia
- Cell death

Secondary insult
- Impaired blood flow
- Impaired oxygenation
- Hypermetabolism
- Hypercatabolism
- Post traumatic seizures
- Coagulopathy
Posttraumatic seizure prophylaxis
Part II
Post traumatic seizures (PTS)

Complication of TBI

- 6-28% TBI patients will experience PTS
- Incidence often correlates with TBI severity

Timing post injury

- Early (≤ 7 days)
- Late (> 7 days)

Early PTS Risk Factors

- GCS ≤ 10
- Immediate seizures (within 24 hours)
- Cortical contusion
- Penetrating head injury
- Depressed skull fracture
- Subdural hematoma
- Epidural hematoma
- Intracerebral hematoma
Why PTS prophylaxis?

Acute adverse effects
- Increased intracranial pressure
- Changes in blood pressure and oxygen delivery
- Excess neurotransmitter release

Long-term consequences
- Accidental injury
- Psychological effects
- Loss of driving privileges
- Chronic epilepsy

Early PTS Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
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<td>GCS ≤ 10</td>
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<tr>
<td>Immediate seizures (within 24 hours)</td>
</tr>
<tr>
<td>Cortical contusion</td>
</tr>
<tr>
<td>Penetrating head injury</td>
</tr>
<tr>
<td>Depressed skull fracture</td>
</tr>
<tr>
<td>Subdural hematoma</td>
</tr>
<tr>
<td>Epidural hematoma</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
</tr>
</tbody>
</table>
Prophylactic Agents

Antiepileptic drug therapy for 7 days post injury

Brain Trauma Foundation Guidelines (2007)
- Phenytoin
- Valproate?

‘Newer’ Agents
- Levetiracetam
**Objective**

“We performed the present investigation to clarify the role of phenytoin in preventing early and late post-traumatic seizures.”

**Design**

Prospective, randomized, placebo-controlled

**Population**

Severe head injury

**Intervention**

Phenytoin: Load 20 mg/kg, further doses adjusted to maintain high therapeutic levels

Intervention continued for 12 months, followed for 24 months

**Endpoint(s)**

Seizure occurrence, early (≤ 7 days) or late (>7 days)
Phenytoin vs Placebo

Early Seizures

- PHT 3.6% ± 1.3% vs Placebo 14.2% ± 2.6%

Late Seizures

- YR 1: PHT 21.5% ± 3.6% vs placebo 15.7% ± 3.2%
- YR 2: PHT 27.5% ± 4.0% vs placebo 21.1% ± 3.7%

Phenytoin Dosing Challenges

Neurocritically ill patient factors
- Hypermetabolic
- Hypercatabolic
- Protein binding alteration

Phenytoin dosing factors
- Narrow therapeutic window
- Variable dosage forms
- Highly protein bound
- Short time to achieve and maintain therapeutic concentrations

Winter-Tozer Equation
\[
\text{Adjusted phenytoin} = \frac{\text{Phenytoin level}}{(0.2 \times \text{albumin}) + 0.1}
\]

REVISED Winter-Tozer Equation
\[
\text{Adjusted phenytoin} = \frac{\text{Phenytoin level}}{(0.25 \times \text{albumin}) + 0.1}
\]
Initial Phenytoin Concentrations In Traumatic Brain Injury Patients

Adjusted Phenytoin Concentrations (mg/dL)

- Supratherapeutic
- Therapeutic
- Subtherapeutic

Time to Level (days)

N = 45

Presented at ASHP Midyear Clinical Meeting, Orlando, FL. December 2013.
# Levetiracetam vs Phenytoin

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare “intravenous levetiracetam to IV phenytoin for seizure prophylaxis after neurological injury”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, randomized, single-blinded</td>
</tr>
<tr>
<td>Population</td>
<td>Patients with severe head injury or subarachnoid hemorrhage (randomized 2:1)</td>
</tr>
</tbody>
</table>
| Intervention | **Levetiracetam group:** Load 20 mg/kg, maintenance 1000 mg q 12 h  
Phenytoin group: Load fosphenytoin 20 mg/kg PE,  
maintenance 5 mg/kg/day (divided q 12 h), adjusted to maintain 10-20 mcg/dl |
| Endpoint(s) | Primary: Clinical adverse effects  
Secondary: Seizures and long term outcomes |
Levetiracetam vs Phenytoin

Results:

- N = 52
  - Levetiracetam, n=34; Phenytoin, n = 18
  - 88.5% (n = 46) patients with severe TBI

- Levetiracetam:
  - Better functional outcome (Disability Rating Score) at 3 months (p = 0.042)
  - Higher Glasgow Outcomes Scale at 6 months (p = 0.039)

- Secondary outcomes:
  - No difference in early seizures: 3/18 (16.7%) vs 5/34 (14.7%); (p = 1)
  - No difference in mortality: 4/18 (22.2%) vs 14/34 (41.2%); (p = 0.227)
PTS Prophylaxis Conclusions

Literature only supports the use of early PTS prophylaxis with risk factors

Use of phenytoin is a recommended choice

Possible utility for levetiracetam

<table>
<thead>
<tr>
<th>Early PTS Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS ≤ 10</td>
</tr>
<tr>
<td>Immediate seizures (within 24 hours)</td>
</tr>
<tr>
<td>Cortical contusion</td>
</tr>
<tr>
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</tr>
<tr>
<td>Depressed skull fracture</td>
</tr>
<tr>
<td>Subdural hematoma</td>
</tr>
<tr>
<td>Epidural hematoma</td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
</tr>
</tbody>
</table>
DVT Prophylaxis

Why?

What?

When?
DVT Prophylaxis

Why?
What?
When?
VTE rates higher in trauma
- DVT occurrence rate = 58% with no prophylaxis

Reasons for increased risk
- Virchow’s Triad
  - Hypercoagulability
    - Increased levels of tissue factor, thrombin
    - Decreased levels of antithrombin, and protein C and S
  - Immobility
  - Delay in initiation of VTE prophylaxis
  - Concomitant injuries (polytrauma)
Incidence of DVT following major trauma

- FACE, CHEST, ABDOMEN: 26/63 (41%)
  - HEAD: 11/16 (69%)
  - SPINE: 8/21 (38%)
  - LOWER EXTREMITIES: 30/43 (70%)
- FACE, CHEST, ABDOMEN: 20/51 (39%)
  - HEAD: 6/12 (50%)
  - SPINE: 20/26 (77%)
  - LOWER EXTREMITIES: 19/26 (73%)
- HEAD: 17/25 (68%)
- SPINE: 19/26 (73%)
- LOWER EXTREMITIES: 69/104 (66%)

N = 243
DVT Risk in TBI Population

Risk factors
- Men
- Age > 55
- Injury severity score > 15
- Subarachnoid hemorrhage
- Lower extremity injury

THROMBOSIS

- Stasis of blood flow
- Vessel wall injury
- Hypercoagulability

DVT Prophylaxis

Why?

What?

When?
CHEST Recommendations

For major trauma patients:

... we suggest use of **LDUH, LMWH, or mechanical prophylaxis**, preferably with IPC, over no prophylaxis.

... at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding **mechanical prophylaxis to pharmacologic prophylaxis** when not contraindicated by lower-extremity injury.

... in whom **LMWH and LDUH are contraindicated**, we suggest **mechanical prophylaxis, preferably with IPC, over no prophylaxis** when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves.

... we do not suggest using an IVC filter for primary VTE prevention.

... we do not suggest that periodic surveillance with venous compression ultrasonography.
DVT Prophylaxis

Why?

LMWH or LDUH?

When?
## Heparin vs Enoxaparin

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>“To better characterize the risk of acute intracranial hemorrhage as well as the effects on DVT and PE at our Level I Trauma center”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Retrospective chart review</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Patients with a Head and Neck Abbreviated Injury Severity Score (HAIS) &gt; 2</td>
</tr>
</tbody>
</table>
| **Intervention** | Sequential compression devices  
Chemoprophylaxis initiated when:  
   - No longer receiving ongoing blood product transfusions  
   - Stable neurologic examination  
   - Repeat head CT with no evidence of active or increased intracranial hemorrhage  
Heparin 5000 units subcutaneously TID  
Enoxaparin 30 mg subcutaneously BID |
| **Endpoint(s)** | N = 386 (enoxaparin, n = 158; heparin, n = 171; none, n = 57) |
# Heparin vs Enoxaparin

<table>
<thead>
<tr>
<th>Complication, n (%)</th>
<th>Chemoprophylaxis (n)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (57)</td>
<td>LMWH (158)</td>
<td>UFH (171)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>27 (47)</td>
<td>8 (5)</td>
<td>27 (16)</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>7 (4)</td>
<td></td>
</tr>
</tbody>
</table>

| Progression of ICH, n (%) | | | |
|---------------------------| | | |
| Total                     | 14 (25) | 20 (13) | 34 (20) |
| Before initiation         | N/A     | 8 (5)   | 14 (8)  |
| After initiation          | N/A     | 0 (0)   | 20 (12) |

N = 386
DVT Prophylaxis

Why?

What?

When?
When to start pharmacologic prophylaxis?

Literature lacking

- < 72 versus > 72 hours
- < 48 hours
- 36 hours post-injury?
- 24 hours after stable CT?
Early Venous Thromboembolism Prophylaxis With Enoxaparin in Patients With Blunt Traumatic Brain Injury

Initiation < 48 hours
**Initiation < 48 hours**

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>“To determine the safety of early enoxaparin for VTE prophylaxis in patients with blunt TBI”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, observational</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Per protocol: Patients with blunt mechanism TBI with enoxaparin given within 48 hours</td>
</tr>
<tr>
<td></td>
<td>Withheld in:</td>
</tr>
<tr>
<td></td>
<td>Intracerebral contusions/hematomas ≥ 2 cm</td>
</tr>
<tr>
<td></td>
<td>Multiple smaller contusions with 1 region of the brain</td>
</tr>
<tr>
<td></td>
<td>Subdural/epidural hematomas ≥ 8 mm thickness</td>
</tr>
<tr>
<td></td>
<td>Persistent ICP &gt; 20 mmHg</td>
</tr>
<tr>
<td></td>
<td>Increase in size or number of brain lesions on follow up CT at 24 hours</td>
</tr>
<tr>
<td></td>
<td>MD reluctance to start</td>
</tr>
<tr>
<td><strong>Endpoint(s)</strong></td>
<td>Intracranial bleeding complications during VTE prophylaxis, hospital mortality, discharge</td>
</tr>
<tr>
<td></td>
<td>Glasgow Outcome Score</td>
</tr>
</tbody>
</table>

### Initiation < 48 hours

<table>
<thead>
<tr>
<th>Endpoint(s)</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding complications during VTE prophylaxis, hospital mortality, discharge Glasgow Outcome Score</td>
<td>N = 525</td>
</tr>
<tr>
<td>Complications:</td>
<td>Glasgow Outcome Score:</td>
</tr>
<tr>
<td>18/525 (3.4%) hemorrhagic CT changes</td>
<td>84.8% good recovery</td>
</tr>
<tr>
<td>6/18 change in treatment or neurologic status</td>
<td>3.6% moderate disability</td>
</tr>
<tr>
<td>Hospital mortality:</td>
<td>6.8% severe disability</td>
</tr>
<tr>
<td>21/525 (1/21 to LMWH, 0.1%)</td>
<td>0.8% persistent vegetative state</td>
</tr>
<tr>
<td></td>
<td>4.0% dead</td>
</tr>
</tbody>
</table>
Early Venous Thromboembolic Event Prophylaxis in Traumatic Brain Injury with Low-Molecular-Weight Heparin: Risks and Benefits

Initiation 48-72 hours
Initiation 48-72 hours

<table>
<thead>
<tr>
<th>Objective</th>
<th>To “(1) examine the occurrence of VTEs and their timing; (2) examine the symptomatic expansion of ICH while on VTE prophylaxis; and (3) compare the efficacy of two prophylactic agents: enoxaparin and dalteparin”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective chart review</td>
</tr>
<tr>
<td>Population</td>
<td>Patients with moderate to severe head injury (GCS 3-12)</td>
</tr>
</tbody>
</table>
| Intervention | Per protocol, initiate within 48-72 hours if: no coagulopathy AND ≥ 2 stable CT scans  
Enoxaparin 30 mg subcutaneously BID  
Dalteparin 5000 units subcutaneously daily  |
| Endpoint(s) | % patients diagnosed with DVTs  
% patients diagnosed on VTE prophylaxis with symptomatic expansion of pre-existing ICH  |
| Results   | N = 287  
% patients diagnosed with DVTs:  
21/287 (7.3%)  
% patients diagnosed with symptomatic expansion of pre-existing ICH:  
1/187 (0.4%), 15 days post-trauma  |

Preliminary Report on the Safety of Heparin for Deep Venous Thrombosis Prophylaxis after Severe Head Injury

Initiation <72 or >72 hours
| **Objective** | To “investigate the safety of early administration of unfractionated heparin for VTE prophylaxis after traumatic brain injury” |
| **Design** | Retrospective chart review |
| **Population** | Patients with severe head injury (Abbreviated Injury Score > 3) |
| **Intervention** | Pneumatic compression devices within 24 hours |
| | Heparin initiated < 72 hours or > 72 hours per trauma and neurosurgery service decision: Heparin 5000 units subcutaneously BID |
| **Endpoint(s)** | increase in intracranial hemorrhage |
| **Results** | N = 64 (Early n = 47, Late n = 17) |
| | Early group – No increase in intracranial bleeding or deterioration of neuro exam |
| | No difference in VTE events |

DVT Prophylaxis Conclusions

Mechanical prophylaxis started as soon as possible with no contraindications

Enoxaparin or heparin may be used for prophylaxis
  ◦ Enoxaparin may be preferred for those with polytrauma

Prophylaxis should be initiated as soon as possible, possibly as soon as 24-48 hours following event/stable head CT
Questions?
laurer.roller@tu.edu
Traumatic Brain Injuries: Pharmacotherapy Challenges

Lauren Roller, PharmD
Critical Care Pharmacist
Highland Hospital

Assistant Clinical Professor
Touro University, College of Pharmacy
Session Code:

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