Pathophysiological stress response following surgery & ERAS

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Chairman ERAS Society

ERAS UK conference 2013
Birmingham November 8 2013
Recovery After Surgery
What are we trying to achieve?

Patient back to preoperative function
• Normal gastrointestinal function
  – Normal food intake
  – Bowel movement
• Pain control
• Mobility
• No complication
The Metabolic Stress Response to Surgery and Trauma
Philosophy
ERAS philosophy: The Patients Journey

Patients Journey

Clinic

Preop

Surgery

Anesthesia

HDU

Ward

Home

Audit compliance & outcomes
ERAS

- Peri-op fluid management
- DVT prophylaxis
- Pre-op counselling
- Early mobilisation
- Perioperative Nutrition
- Body heating devices
- Oral analgesics/NSAID’s
- Prevention of ileus/prokinetics
- Early removal of catheters/drains
- Short acting anesthetics
- No - premed
- No bowel prep
- CHO - loading/ no fasting
- Incisions
- No NG tubes

Fearon et al, Clin Nutr 2005
ERAS
Securing modern care

**Surgeon:**
- No bowel prep
- Food after surgery
- No drains
- Early removal u-catheter
- No iv fluids, no lines
- Early discharge

*All evidence based!*

**Anesthetist:**
- Carbohydrates no fasting
- No premedication
- Thoracic Epidural Anesthesia (open)
- Balanced fluids
- Vasopressors
- No or short acting opioids
ERAS team approach

- Surgeon
- Anesthetist
- HDU specialist
- Ward nurses
- Anesthesia nurses
- Physiotherapist
- Dietitian
- Management

Team work:
- Training
- Implementing
- Planning
- Auditing
- Updating
- Reporting
- Research
ERAS works!
ERAS Meta analysis

ERAS: shorter length of stay by 2.5 days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ERAS</th>
<th>TC</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2003</td>
<td>4</td>
<td>2.1</td>
<td>-3.00 [-4.56, -1.44]</td>
<td></td>
</tr>
<tr>
<td>Delaney 2003</td>
<td>5.2</td>
<td>3</td>
<td>-0.60 [-1.95, 0.75]</td>
<td></td>
</tr>
<tr>
<td>Gatt 2005</td>
<td>6.6</td>
<td>19</td>
<td>-2.40 [-5.22, 0.42]</td>
<td></td>
</tr>
<tr>
<td>Khoo 2007</td>
<td>5</td>
<td>7</td>
<td>-2.00 [-7.64, 3.64]</td>
<td></td>
</tr>
<tr>
<td>Muller 2009</td>
<td>6.7</td>
<td>10.3</td>
<td>-3.60 [-5.17, -2.03]</td>
<td></td>
</tr>
<tr>
<td>Serclova 2009</td>
<td>7.4</td>
<td>3.1</td>
<td>-3.00 [-3.92, -2.08]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>226</td>
<td>226</td>
<td>100.0%</td>
<td>-2.51 [-3.54, -1.47]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.80; Chi² = 11.04, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 4.76 (P < 0.000001)
ERAS Meta analysis

ERAS: Reduce complications by 50%

Varadhan et al, Clin Nutr 2010
How does ERAS work?

Mechanisms
3 new guidelines 2012

Multimodal


J. Nygren · J. Thuerer · F. Carli · K. C. H. Fearon · S. Norderval · D. N. Lobo · O. Ijungqvist · M. Soop · J. Ramirez
Integration of care

- Peri-op fluid management
- Epidural Anaesthesia
- Remifentanyl
- DVT prophylaxis
- No - premed
- Cho loading/
  no fasting
- Early bowel prep
- Early mobilisation
- Pre-op conceling
- Perioperative
  nutrition
- Bairthugger
- Oral analgesics/
  NSAID's
- Prevention of ileus/
  prokinetics
- Incisions
- No NG tubes
- Early removal of catheters/drains

How does ERAS work?

Mechanisms

Insulin
Insulin & Recovery

Insulin: main anabolic hormone involved in
• All parts of metabolism
  – Glucose control
  – Fat metabolism
  – Protein
• Regulator of return of key functions
• Central to development of complications
• Affected by many perioperative treatments
Insulin & Recovery

Insulin: main anabolic hormone involved in

- All parts of metabolism
  - Glucose control
  - Fat metabolism
  - Protein

- Regulator of return of key functions
- Central to development of complications
- Affected by many perioperative treatments

- Insulin resistance: a key for understanding and enhancing recovery
Postoperative Insulin resistance

Definition:
Below normal metabolic effect of insulin
- Glucose uptake
- Reduction in glucose production
- Lipolysis
- Protein breakdown / balance
Insulin sensitivity falls with the magnitude of surgery

Adopted from Thorell et al: Curr Opin Clin Nutr Metab Care 1999

Reduction in Insulin Sensitivity (%)

- Lap cholecystectomy
- Open hernia repair
- Open cholecystectomy
- Open colorectal surgery

Postop / Preop M-value x 100 (%)

$P < 0.001$, ANOVA

$n = 6-13$

More Insulin Resistance
Independent factors predicting length of stay

- Type of surgery
- Perioperative blood loss
- Postoperative insulin resistance

\[ R^2 = 0.71, \ p < 0.01 \]
Glucose uptake

Insulin regulated
Concentration regulated

Glucose uptake occurs in various tissues:
- Muscle
- Liver
- Fat
- Neural tissue
- Blood cells
- Endothel
Glucose uptake - meal

Insulin regulated
Concentration regulated

Muscle

Liver

Storage

[B-Glucose]

Kidney

Blood cells

Endothel

Fat

Neural tissue
Glucose uptake - stress

Liver

Muscle

Fat

[Glucose]

Insulin regulated
Concentration regulated

Kidney

Blood cells

Endothel

Neural tissue
Driving forces for hyperglycemia after surgery

<table>
<thead>
<tr>
<th>Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td><strong>Glucose production</strong></td>
</tr>
<tr>
<td><strong>Peripheral glucose uptake</strong></td>
</tr>
<tr>
<td>GLUT4 translocation</td>
</tr>
<tr>
<td>Glycogen formation</td>
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</table>

Adopted from Ljungqvist et al, Clin Nutr 2001
# Driving forces for hyperglycemia after surgery similar to diabetes

<table>
<thead>
<tr>
<th></th>
<th>Postop</th>
<th>Type 2 DM</th>
</tr>
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<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
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Adopted from Ljungqvist et al, Clin Nutr 2001
Normalizing insulin action normalizes metabolism

Insulin infusion to normalize:
• Blood glucose

Also controlled:
• FFA
• Urea excretion
• Substrate utilization after major surgery

Insulin resistance the key to catabolism

Glucose uptake - stress

Too little

Liver

Too much

Muscle

Fat

Neural tissue

Blood cells

Endothel

Insulin regulated

Concentration regulated
Insulin resistance muscle

- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism
Insulin resistance muscle

- Reduced glucose uptake
- Reduced glycogen storage
- Increased protein catabolism

Energy supply

Lean body mass

- Muscle function

Mobilisation
Impaired Recovery

<table>
<thead>
<tr>
<th>Postop (days)</th>
<th>Tissues/cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>muscle</td>
</tr>
<tr>
<td>Infections</td>
<td>leukocytes</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>blood vessels</td>
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<tr>
<td>Renal failure</td>
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Glucose uptake - stress

Insulin regulated
Concentration regulated

Too little
Muscle
Fat

[Glucose]

Too much
Liver
Kidney
Blood cells
Endothel

Neural tissue
## Complications

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<td>Muscle weakness</td>
<td>muscle</td>
</tr>
</tbody>
</table>
Why these organs/cells?

Tissues unprotected to glucose uptake:

- Uncontrolled inflow of glucose
- No storage
- Overflow of glycolysis
- ROS production
- Block of glycolysis & Krebs cycle
- Altered gene expression
- Enhanced inflammatory response
- Vicious circle
Vicious circle

Stress of surgery

Stress hormones

Cytokines

Insulin resistance

Hyperglycemia

Enhanced inflammation

ROS production
Insulin important for wound healing

- 6 patients studied twice, >40% burn injury
- Placebo – randomised - cross over design
- Hyperinsulinemia
  - 400-900 microunits/ml for 7 days or placebo
- Glucose infusion to normoglycemia

- Donor-site healing time reduced
  - from 6.5 to 4.7 days, p < 0.05

EJ Pierre et al, J Trauma 1998
Glucose levels in ERAS & outcomes after surgery

- 120 Consecutive patients
- Colorectal surgery
- No history of diabetes
- Preop HbA1c – above or below 6.1
- 26% pathologically high (≥ 6.1 mM)
- Glucose 5 times daily postop
- CRP and complications (30 day follow up)

Gustafsson et al, BJS 2009: 96; 1358-64
Glucose after major elective surgery

N = 120
1500 kcal/d

Gustafsson et al, BJS 2009: 96; 1358-64
HbA1c, Glucose control and postop complications

Gustafsson et al, BJS 2009: 96; 1358-64

OR 2.9
P < 0.05

OR 2.3
P = 0.13
Postoperative insulin resistance increase the risk for complications

273 patients open cardiac surgery, insulin sensitivity determined at the end of op

<table>
<thead>
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<th>Complication</th>
<th>OR for every decrease by 1 mg/kg/min (Insulin sensitivity)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.33 (0.94-5.78)</td>
<td>0.067</td>
</tr>
<tr>
<td>Major complication</td>
<td>2.23 (1.30-3.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>Severe infection</td>
<td>4.98 (1.48-16.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>Minor infection</td>
<td>1.97 (1.27-3.06)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

The ORs were adjusted for potential confounders

Sato et al, JCEM 2010; 95: 4338-44
Epidural Anaesthesia

Prevention of ileus/prokinetics

Peri-op fluid balance

DVT prophylaxis

Pre-op counselling

Early mobilisation

Pre-op counselling

Early postop oral feeding

Maintaining body temperature

Oral analgesics/NSAID’s

Prevention of ileus/prokinetics

Short acting anaesthetics

No - premed

No bowel prep

Preop CHO/no fasting

Surgical technique

No NG tubes

Early removal of catheters/drains

Fearon et al, Clin Nutr, 2005
ERAS

- Epidural Anaesthesia
- Short acting anaesthetics
- Peri-op fluid balance
- DVT prophylaxis
- Pre-op counselling
- Early mobilisation
- Early postop oral feeding
- Maintaining body temperature
- Oral analgesics/NSAID’s
- Prevention of ileus/prokinetics
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- No - premed
- No bowel prep
- Preop CHO/no fasting
- Surgical technique
- No NG tubes

Fearon et al, Clin Nutr, 2005
ERAS elements to reduce insulin resistance

Preoperative
- Preoperative carbohydrates
- Epidural anesthesia

Postoperative
- Pain control
- Early postop feeding
Preoperative CHO reduces postop insulin resistance

Nygren et al: Curr Opin Clin Nutr Metab Care 2001
Preoperative carbohydrates retains lean body mass (MAC)

Yuill et al, Clin Nutr 2005

![Graph showing the effect of carbohydrates on lean body mass with a P <0.05 significance level.](image)
Preoperative carbohydrates reduces protein losses and improves muscle strength

EDA reduces postoperative insulin resistance

Uchida, Br J Surg 1988

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**EDA** reduces postoperative insulin resistance. The graph illustrates the postoperative change in various hormones and insulin sensitivity. The red bars represent IV Opiates, and the blue bars represent EDA. Statistical significance is indicated with *p<0.05* and **p<0.01** marks.
EDA + Preoperative CHO to control glucose during enteral feeding

Insulin sensitivity improved with pre op Carb, EDA + post op feed

Epidural - less paralysis

EDA vs. Iv opiates

Jorgensen Cochr Database Syst Rev 2004
ERAS: oral intake development (mean intake postop day 1-4)
Insulin sensitivity
Day before surgery

ERAS Care

Traditional care

Insulin sensitivity
- Dinner, normal sleep
- Bowel prep
- No nutrition
Insulin sensitivity
Morning of surgery

ERAS Care

Dinner, normal sleep

Carbohydrate treatment

Overnight fasting

Bowel prep
No nutrition

Traditional care
Insulin sensitivity
Morning of surgery

ERAS Care

Dinner, normal sleep

Carbohydrate treatment

Overnight fasting

Bowel prep
No nutrition

Traditional care
Insulin sensitivity
Anesthesia start

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural

Preoperative sedation
Overnight fasting
Bowel prep
No nutrition

Traditional care
Insulin sensitivity

Reaction to surgery

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural

Preoperative nutrition
Overnight
Bowel prep
No nutrition

Greater drop without Epidural

Traditional care
Insulin sensitivity

Afternoon of surgery

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural
Immediate feeding & mobilisation

NPO iv low caloric fluids

Preoperative medication

Overnight
Bowel prep
No nutrition

Traditional care

ERAS Care
Insulin sensitivity

Days after surgery

- **ERAS Care**
  - Dinner, normal sleep
  - Carbohydrate treatment
  - Thoracic Epidural
  - Immediate feeding & mobilisation

- **Traditional care**
  - Bowel prep
  - No nutrition
  - Overnight
  - Preoperative sedation
  - NPO iv low caloric fluids
  - Slow return to feeding and mobilisation

- **Days - weeks**
Insulin sensitivity

Days after surgery

ERAS Care

Dinner, normal sleep
Carbohydrate treatment
Thoracic Epidural
Immediate feeding & mobilisation

Oral feeding & mobilisation

Slow return to feeding and mobilisation

Days - weeks

Insulin sensitivity

Traditional care

Bowel prep
No nutrition

Preoperative sedation

Overnight

NPO iv low caloric fluids

Ljungqvist JPEN 2012
Metabolic response to surgery in traditional perioperative care

![Bar graph showing postoperative change (%): N losses, N balance, Energy exp, Glucose, Insulin, Insulin sens. The graph indicates significant changes in glucose and insulin levels compared to baseline.]

**Traditional**
Metabolic response to surgery in traditional perioperative care vs. ERAS protocols

Postoperative change (%)

- N losses
- N balance
- Energy exp
- Glucose
- Insulin
- Insulin sens

Traditional
ERAS protocols
Conclusions

• Minimizing metabolic stress is key to improved recovery
• Insulin resistance is central
• ERAS principles works in all major surgery
• Many ERAS components reduce metabolic stress
• Combining ERAS elements for best results
2nd World ERAS Congress

• Valencia Spain
• April 23-26, 2014

• Multiprofessional
• Multi disciplinary
• Patient, Practice & Outcomes

• Henrik Kehlet Lecture:
  – Economics of ERAS / A Senagore
• ERAS Lecture:
  – Postoperative cognition / S Newman
• World leaders in ERAS