ENHANCED RECOVERY AFTER SURGERY (ERAS) – AN ANESTHESIOLOGIST PERSPECTIVE
Dr. Vijay Tarnal
Director of Neuro-Anesthesia, Michigan Medicine

ERAS in Spine Surgery - Anesthesia Specific Elements
Dr Vijay Tarnal MBBS, FRCA
Clinical Associate Professor
Director, Division of Neuroanesthesiology
Department of Anesthesiology
Michigan Medicine
Outline

- Preoperative Fasting and Carbohydrate Loading
- Use of Tranexamic Acid in Spine Surgery
- Role of Methadone & Regional Blocks in Multi-modal Analgesia

Principles of ERAS

- Multidisciplinary team around a patient
- Multimodal approach to resolving issues that delay recovery & cause complications
- A scientific, evidence-based approach to care protocols
- A change in management using interactive & continuous audit

Ljungqvist et al; JAMA Surg. 2017
ERAS PROTOCOLS

ERAS Overview for Spinal Fusion

Debno et al; Neurosurg Focus 2019
Outline

• Preoperative Fasting and Carbohydrate Loading
• Use of Tranexamic Acid during Spine Surgery
• Role of Methadone & Regional Blocks in Multi-modal Analgesia

Pre-Operative Fasting

✅ NPO overnight practice since 1940s
💧 NPO overnight - Reduce risk of aspiration
🧴 Volume & content of gastric content
🧱 pH of gastric content
📷 Clinical picture of aspiration
🧱 Stricter guidelines for overnight NPO - Now questioned

1 Bannister et al; Anesthesiology 1962
2 Warner et al; Anesthesiology 1993
Pulmonary Aspiration: Facts & Fiction

- Gastric emptying of clear, non-caloric fluids—extremely fast exponential curve
- Anxiety & Stress—Delay gastric emptying
- Anxiolytics—No difference to gastric emptying
- Solids—Linear curve
- National Anesthesia Societies—Liberal approach to NPO
  ✓ Clear Fluids—2hrs
  ✓ Light Meal—6hrs
  ✓ Fatty Meal—8hrs

Effect Of Surgical Stress & NPO On Metabolism

Catabolic Pathway

- ↑Immunosuppression & Insulin resistance
- ↓Glucose uptake
- ↑Gluconeogenesis
- ↑Catecholamine surge
- ↑Cortisol, Glucagon, GH
- ↑IL-1, IL-6
- ↑Post-Op lean tissue loss: Strength, Mobilization, Wound healing, & Respiratory mechanics

References:
1. Ljungqvist et al; BJS 2003
2. Erskine et al; J Physiol 1981
Pre-Operative Carbohydrate Loading

12 patients for elective open cholecystectomy
Randomized to receive iv dextrose infusion during preop overnight fasting period
Measure- Insulin sensitivity (M value)
Findings:
Pre-op: M value similar in both groups
Post-Op M value:
Control group- 55+/−3%
Glucose group- 32+/−4% (p value<0.01)
Conclusion: Pre-op CHO loading reduces insulin resistance


Insulin Resistance: Fasting v Fed State

*P < 005 versus control

46 Ljungqvist et al; J Am Coll Surg 1994
47 Nygren et al; Am J Physiol 1998
48 Nygren et al; Clin Nutr 1998
49 Soop et al; Am J Physiol Endocrinol Metab 2001
Insulin Resistance - Factor of Clinical Importance?

- Insulin Resistance - Transient phenomenon
- Glucose uptake reduced in part due to a lesser response by GLUT-4 transporters to insulin
- Lasts about 3 weeks post-op after uncomplicated surgery
- Resemble state of untreated NIDDM
- Degree of insulin resistance - Independent Factor in predicting of LOS

Effect of Surgical Stress & NPO On Metabolism

- Insulin Resistance central metabolic change during surgical stress and is directly proportional to the magnitude of procedure
- Independent risk factor influencing LOS Post-Op

References:

- Thorell et al; Curr Opin Clin Nutr Metab Care 1999
- Thorell et al; Br J Surg 1994
- Ljungqvist et al; Clin Nutr 2001
- van der Berghe G; NEJM 2001
Methods
- 26 patients (CABG) & 12 patients (spine surgery)
- Randomized to receive 800 mL of an oral CHO supplement the evening before and 400 mL 2 hours before surgery (CHO) or to fasting per standard hospital protocol (FAST)

Outcomes
- Baseline and postop Insulin sensitivity
- IL-6, CRP, & FFA levels determined at baseline, postoperatively, & 24, 48, & 72 hours after surgery
- Subjective feelings of well-being were measured immediately before surgery
- Intra- and postop outcomes were documented
CHO Loading

17 randomized controlled trials with a total of 1,445 patients until 2011
CHO drinks significantly improved insulin resistance
Improved indices of patient comfort (hunger, thirst, anxiety, malaise)
No conclusions on preservation of muscle mass
No aspiration events reported
Probably safe with a positive influence on a wide range of perioperative markers of clinical outcome

11/3/2020

17

Current Literature On CHO Loading

- 26 publications on CHO load
- 17 RCTs; 3 Prospective Observational studies; 6 retrospective series with case-control comparison
- Preoperative CHO loading is safe
- No difference in infection risk or LOS
- Effective for maintaining a euglycemic state, no significant adjustment of the risk of post-op infectious complications

Gianotti et al; Curr Opin Clin Nutr Metab Care 2020

Pre-Op CHO Loading by Recommendation & Evidence

Ackerman et al; Nutr Clin Pract. 2020
Pre-Operative Carbohydrate Loading

50G complex carbohydrate in 400mL

Reduce insulin sensitivity by 50%

Appropriate osmolality for sufficient gastric emptying

International Recommendations for Intake of Solids and Liquids Preoperatively

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Anesthesia Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast for liquids, h</td>
<td>Canada (2015)</td>
</tr>
<tr>
<td>Fast for solids, h CHO fluids</td>
<td>Europe (2011)</td>
</tr>
<tr>
<td>≤6 light meal; ≤8 meat or fatty food</td>
<td>United States (2011)</td>
</tr>
<tr>
<td>No comment</td>
<td></td>
</tr>
<tr>
<td>≥6 solid food</td>
<td></td>
</tr>
<tr>
<td>Consider preoperative CHO drinks</td>
<td></td>
</tr>
<tr>
<td>≥6 light meal; ≤8 fatty food</td>
<td></td>
</tr>
<tr>
<td>No comment</td>
<td></td>
</tr>
</tbody>
</table>

CHO, carbohydrate.


<table>
<thead>
<tr>
<th>Product</th>
<th>Location Available</th>
<th>Volume, mL</th>
<th>Osmolality, mOsm/kg</th>
<th>Maltodextrin, g</th>
<th>% CHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>preOp</td>
<td>Europe, United Kingdom</td>
<td>400</td>
<td>285</td>
<td>40</td>
<td>12.0</td>
</tr>
<tr>
<td>Clearchef</td>
<td>United States</td>
<td>355</td>
<td>270</td>
<td>44</td>
<td>12.0</td>
</tr>
<tr>
<td>ONS 300</td>
<td>Germany</td>
<td>300</td>
<td>266</td>
<td>50</td>
<td>16.6</td>
</tr>
<tr>
<td>ONS 400</td>
<td>Germany</td>
<td>400</td>
<td>266</td>
<td>50</td>
<td>12.5</td>
</tr>
<tr>
<td>Preload</td>
<td>United Kingdom</td>
<td>400</td>
<td>266</td>
<td>47.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Arginaid H2O</td>
<td>Japan</td>
<td>250</td>
<td>200</td>
<td>52</td>
<td>18.0</td>
</tr>
<tr>
<td>Maxjul</td>
<td>United Kingdom, Europe</td>
<td>420</td>
<td>420</td>
<td>43.25</td>
<td>32.0</td>
</tr>
</tbody>
</table>
Summary - CHO Loading

**Recommendations**
- 12% complex CHO drink (400mL) 2h- SAFE
- ERAS guidelines strongly recommend the routine use of carbohydrate loading
- ↓ Perioperative hyperglycemia, insulin resistance & catabolism
- Improves subjective well-being and comfort

**Limitations**
- Evidence extrapolated for some procedures
- ?LOS
- Significant costs of CHO loading
- Evidence is weak in DM & delayed gastric emptying

Outline

- Preoperative Fasting and Carbohydrate Loading
- Use of Tranexamic Acid in Spine Surgery
- Role of Methadone & Regional Blocks in Multi-modal Analgesia
Risk Factors for Increased Bleeding and Transfusion

- Anterior Spinal instrumentation and Fusion
- Multilevel fusion (>3 levels)
- Deformity, Tumor, Trauma
- Prolonged operative time
- Sacral involvement and posterior approach

**Predictive Model for Transfusion (Lenoir et al)**
1. Age > 50 yrs
2. Pre-Op Hgb < 12 gm%
3. Fusion > 2 levels
4. Transpedicular osteotomy

- Ristagno et al; BMC Anesthesiol. 2018
- Morcos et al; Spine 2018
- Lenoir et al; Anesthesiology 2009

Fibrinolysis Pathway

- Vessel wall
- Endothelial activation
- Endothelial cells
- Prothrombin
- Thrombin
- Xa-Va
- X
- TF-VIIa
- Vascular injury
- Fibrinogen
- Plasminogen
- Urokinase
- Contact activation
- Plasmin
- Plasminogen activator (tPA)
- Kallikrein
- α2-antiplasmin

- Levy et al; Anesthesiology 2017
Fibrinolysis and Antifibrinolytics

Effects of Fibrinolysis

Fibrinolysis cleaves GPIb & GP IIb/IIIa receptors on platelets Coagulopathy

Plasmin initiates Proinflammatory responses

Multi-Organ System Failure

Levy et al; Anesthesiology 2017

Caesarman-Maus et al; Br J Haematol 2005
Medcalf et al; J Thromb Haemost 2007
Karkouti et al; Anesth Analg 2010
Tranexamic Acid

- Lysine Analogue
- Competitive inhibitor of plasminogen activation
- Higher doses - Non-Competitive inhibitor of plasmin
- TXA is 7-10 times more potent than Amicar with more sustained antifibrinolytic activity
- Elimination 1/2 life 2h
- Essential Medication List - WHO

Mode of Action of Lysine Analogues (Amicar and TXA)

Verstraete M et al; Drugs 1985
Nilsson et al; J Clin Pathol Suppl

Mannucci et al; NEJM 2007
1Wong et al; Anesth Analg 2008

- **TXA in Spine Surgery**

**Objective:** Efficacy of TXA in reducing blood loss and transfusion in patients undergoing spine surgery

**Methods:** Prospective, RCT, Double blind multicenter study

147 patients included in analysis

**TXA v Placebo (10mg/kgloading; 1mg/kg/hr maintenance)**

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**Table 1. Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 73)</td>
<td>(n = 74)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.8 ± 16.2</td>
<td>50.0 ± 16.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>52/21</td>
<td>48/26</td>
<td>0.408</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.3 ± 12.5</td>
<td>165.2 ± 10.2</td>
<td>0.132</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.9 ± 17.2</td>
<td>73.9 ± 16.1</td>
<td>0.717</td>
</tr>
<tr>
<td>ASA status: I/II/III</td>
<td>5/43/24</td>
<td>14/35/24</td>
<td>0.166</td>
</tr>
<tr>
<td>No. (%) of patients with osteotomy</td>
<td>13 of 73 (17%)</td>
<td>17 of 74 (22%)</td>
<td>0.437</td>
</tr>
<tr>
<td>No. (%) of patients with revision</td>
<td>19 of 73 (26%)</td>
<td>24 of 74 (32%)</td>
<td>0.393</td>
</tr>
<tr>
<td>No. of levels</td>
<td>4.7 ± 4.6</td>
<td>4.8 ± 4.3</td>
<td>0.910</td>
</tr>
<tr>
<td>Level groups: I/II/III</td>
<td>35/17/21</td>
<td>32/19/23</td>
<td>0.848</td>
</tr>
<tr>
<td>No. (%) of patients predonated</td>
<td>39 of 73 (53%)</td>
<td>45 of 74 (60%)</td>
<td>0.366</td>
</tr>
<tr>
<td>No. of units predonated</td>
<td>1.0 ± 0.9</td>
<td>1.1 ± 0.9</td>
<td>0.499</td>
</tr>
<tr>
<td>No. (%) of patients given erythropoietin</td>
<td>20 of 73 (27%)</td>
<td>25 of 74 (33%)</td>
<td>0.401</td>
</tr>
<tr>
<td>Amount of erythropoietin given (IU)</td>
<td>64760 ± 34000</td>
<td>79130 ± 36420</td>
<td>0.185</td>
</tr>
</tbody>
</table>

Values are presented as mean ± sd (standard deviation) or proportion (%). Distribution of the number of patients among the 3 centers: Toronto Western Hospital: 107 St. Michaels’s Hospital: 17, Trillium Health Center: 23.

1Wong et al; Anesth Analg 2008
**TXA in Spine Surgery**

- Total Peri-Op blood loss 25-30% less in TXA group
- TXA decreased EBL by approx. 580mL
- Blood Loss: positive relationship to duration of surgery & # of vertebrae fused
- LOS similar both groups
- DVT (1 case in placebo group)

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**CRASH-2 Trial**

- **Question**
  - Does early administration of a short course of TXA affect mortality, incidence of occlusive events & blood transfusion?

- **Design**
  - Multicenter, randomized, double blinded, placebo controlled
  - 20,000+ patients enrolled
  - Adults with trauma within 8h of incident (significant or at risk for significant hemorrhage)

- **Intervention**
  - Loading dose of 1G TXA over 10min followed by 1G over 8h

- **Outcomes**
  - Death in hospital within 4wks of injury
  - Receipt of transfusion, surgical intervention, vascular occlusive episodes, dependency at hospital discharge

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1. Wong et al; Anesth Analg 2008
2. Shakur et al; Lancet 2010
CRASH-2 Trial

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Measure</th>
<th>TXA</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>ARR (95% CI)</th>
<th>NNT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all cause)</td>
<td>14.5%</td>
<td>16.0%</td>
<td>0.91 (0.85 – 0.97)</td>
<td>1.5% (0.49 – 2.47)</td>
<td>68</td>
<td>0.0035</td>
<td></td>
</tr>
<tr>
<td>Death (by subgroup)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>4.9%</td>
<td>5.7%</td>
<td>0.85 (0.76 – 0.96)</td>
<td>0.8% (0.22 – 1.46)</td>
<td>119</td>
<td>0.0077</td>
<td></td>
</tr>
<tr>
<td>Vascular occlusion</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.69 (0.44 – 1.07)</td>
<td>0.2% (-0.03 – 0.23)</td>
<td>673</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>2.1%</td>
<td>2.3%</td>
<td>0.90 (0.75 – 1.08)</td>
<td>0.2% (-0.17 – 0.64)</td>
<td>423</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Head injury</td>
<td>6.0%</td>
<td>6.2%</td>
<td>0.97 (0.87 – 1.08)</td>
<td>0.2% (-0.49 – 0.83)</td>
<td>573</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td>1.3%</td>
<td>1.4%</td>
<td>0.94 (0.74 – 1.20)</td>
<td>0.1% (-0.24 – 0.39)</td>
<td>1273</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

Death = in hospital death within 28 days; RR = relative risk; CI = confidence interval; ARR = absolute risk reduction; NNT = number needed to treat; p = p-value

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Measure</th>
<th>TXA</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>ARR (95% CI)</th>
<th>NNT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular occlusive events</td>
<td>1.7%</td>
<td>2.0%</td>
<td>0.84 (0.68 – 1.02)</td>
<td>0.3% (-0.05 – 0.69)</td>
<td>316</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>47.9%</td>
<td>48.0%</td>
<td>1 (0.97 – 1.03)</td>
<td>0.1% (-1.2 – 1.57)</td>
<td>540</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Receipt of blood products</td>
<td>50.4%</td>
<td>51.3%</td>
<td>0.98 (0.96 – 1.01)</td>
<td>0.9% (-0.49 – 2.27)</td>
<td>113</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Dependency</td>
<td>TXA</td>
<td>Control</td>
<td>RR (95% CI)</td>
<td>ABI (95% CI)</td>
<td>NNT</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>14.7%</td>
<td>13.3%</td>
<td>1.11 (1.04 – 1.19)</td>
<td>1.4% (0.53 – 2.45)</td>
<td>68</td>
<td>0.0023</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>12.9%</td>
<td>12.6%</td>
<td>1.02 (0.95 – 1.09)</td>
<td>0.3% (-0.70 – 1.14)</td>
<td>460</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Fully Dependent</td>
<td>6.9%</td>
<td>6.7%</td>
<td>1.03 (0.93 – 1.14)</td>
<td>0.25 (-0.49 – 0.90)</td>
<td>492</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>

Vascular occlusive events = MI, Stroke, PE, DVT; Dependency = 5-point Modified Oxford Handicap Scale; ABI = absolute benefit increase;

Shakur et al; Lancet 2010

Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis

- **Study Selection**
  - RCT comparing TXA v no TXA v Placebo
  - Systematic review & meta-analysis

- **Objective**
  - Assess effect of TXA on blood transfusion, Thromboembolic events & Mortality in surgical patients

- **Results**
  - 129 trials, 10,488 patients (1972-2011)
  - TXA reduced probability of receiving transfusion by a third (RR 0.62 CI 0.58-0.65; p<0.001)
  - Effect of TXA on MI, Stroke, DVT & PE – uncertain
  - Cumulative meta-analysis- TXA reduced need for transfusion

Ker et al; BMJ 2011
Effect of TXA on Surgical Bleeding

Ker et al; BMJ 2011

Effect of TXA on Transfusion, TE, and Mortality

Ker et al; BMJ 2011

Table 2: Meta-analysis of effect of tranexamic acid on risk of blood transfusion, stratified by type of surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No of events (tranexamic acid/control)</th>
<th>Pooled risk ratio (95% CI)</th>
<th>P value*</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>622/835</td>
<td>0.65 (0.60 to 0.70)</td>
<td>&lt;0.001</td>
<td>60</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>296/462</td>
<td>0.55 (0.49 to 0.61)</td>
<td>&lt;0.001</td>
<td>83</td>
</tr>
<tr>
<td>Hepatic</td>
<td>29/54</td>
<td>0.52 (0.39 to 0.68)</td>
<td>&lt;0.001</td>
<td>93</td>
</tr>
<tr>
<td>Urological</td>
<td>40/60</td>
<td>0.66 (0.48 to 0.91)</td>
<td>0.01</td>
<td>2</td>
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<tr>
<td>Vascular</td>
<td>11/19</td>
<td>0.58 (0.34 to 0.99)</td>
<td>0.05</td>
<td>—</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>17/50</td>
<td>0.86 (0.48 to 1.54)</td>
<td>0.61</td>
<td>65</td>
</tr>
<tr>
<td>Cranial and orthognathic</td>
<td>52/76</td>
<td>0.63 (0.45 to 0.86)</td>
<td>0.004</td>
<td>46</td>
</tr>
</tbody>
</table>

*Test for effect.

Ker et al; BMJ 2011
### Effect of TXA on Transfusion, TE, and Mortality

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Events (tranexamic acid/control)</th>
<th>Pooled risk ratio (95% CI)</th>
<th>P value*</th>
<th>I² (%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>All trials 106/7152</td>
<td>0.62 (0.58 to 0.65)</td>
<td>&lt;0.001</td>
<td>89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 49/609</td>
<td>0.66 (0.62 to 0.74)</td>
<td>&lt;0.001</td>
<td>55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adequate blinding 84/7152</td>
<td>0.60 (0.59 to 0.60)</td>
<td>&lt;0.001</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>All trials 23/35</td>
<td>0.66 (0.42 to 1.09)</td>
<td>0.11</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 16/25</td>
<td>0.70 (0.39 to 1.28)</td>
<td>0.22</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate blinding 18/33</td>
<td>0.59 (0.36 to 0.96)</td>
<td>0.04</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>All trials 23/16</td>
<td>1.14 (0.65 to 2.00)</td>
<td>0.65</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 5/4</td>
<td>1.18 (0.36 to 3.83)</td>
<td>0.78</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate blinding 23/16</td>
<td>1.14 (0.65 to 2.00)</td>
<td>0.65</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>All trials 25/29</td>
<td>0.86 (0.53 to 1.39)</td>
<td>0.56</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 13/14</td>
<td>0.92 (0.45 to 1.85)</td>
<td>0.81</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate blinding 18/22</td>
<td>0.82 (0.46 to 1.44)</td>
<td>0.49</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>All trials 4/8</td>
<td>0.61 (0.25 to 1.47)</td>
<td>0.27</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 1/3</td>
<td>0.50 (0.10 to 2.75)</td>
<td>0.44</td>
<td>0.80</td>
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</tr>
<tr>
<td></td>
<td>Adequate blinding 4/6</td>
<td>0.70 (0.36 to 1.87)</td>
<td>0.48</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td>All trials 20/34</td>
<td>0.61 (0.38 to 0.94)</td>
<td>0.04</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well controlled trials 9/15</td>
<td>0.67 (0.35 to 1.34)</td>
<td>0.25</td>
<td>0.95</td>
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<tr>
<td></td>
<td>Adequate blinding 20/34</td>
<td>0.61 (0.38 to 0.94)</td>
<td>0.04</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

*Test for effect.

---

### Intra-Operative Blood Loss

#### Table 1: Meta-analysis of effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TXA Group Mean</th>
<th>SD</th>
<th>Control Group Mean</th>
<th>SD</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neipokroz 2001</td>
<td>2,453</td>
<td>1,265</td>
<td>2,703</td>
<td>1,297</td>
<td>-250.00</td>
<td>-1046.53, 546.53</td>
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</tr>
<tr>
<td>Sethna 2000</td>
<td>1,220</td>
<td>530</td>
<td>2,085</td>
<td>1,188</td>
<td>2.7</td>
<td>850.00, -1408.15, -301.80</td>
<td></td>
</tr>
<tr>
<td>Wong 2005</td>
<td>1,203</td>
<td>1,060</td>
<td>1,600</td>
<td>1,301</td>
<td>74.2</td>
<td>5.23, -397.50, -39.40, 13.60</td>
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</tr>
<tr>
<td>Elwalid 2008</td>
<td>311.25</td>
<td>412.49</td>
<td>584.89</td>
<td>707.3</td>
<td>273.43</td>
<td>584.67, 37.06</td>
<td></td>
</tr>
<tr>
<td>Farrokhzad 2011</td>
<td>1,288.9</td>
<td>690</td>
<td>1,335.9</td>
<td>550</td>
<td>58.8</td>
<td>38.6, -67.00, 213.55</td>
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</tr>
<tr>
<td>Kim 2000</td>
<td>541.11</td>
<td>850</td>
<td>964.21</td>
<td>214</td>
<td>11.97</td>
<td>-309.00, 167.24, 50.76</td>
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</tr>
<tr>
<td>Hang C2011</td>
<td>641.11</td>
<td>128.4</td>
<td>708.10</td>
<td>107.3</td>
<td>31.2</td>
<td>-37.00, -123.25, 10.75</td>
<td></td>
</tr>
<tr>
<td>Tatsuzumoto 2011</td>
<td>49.1</td>
<td>30.6</td>
<td>63.4</td>
<td>53</td>
<td>20.34</td>
<td>13.41, -14.30, 41.12, 12.52</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>253</td>
<td>248</td>
<td>100.08</td>
<td>-128.28, -222.73, -33.84</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 6626.42; Chi² = 22.23, df = 7 (P = 0.002); I² = 69%

Test for overall effect: Z = 2.66 (P = 0.008)

---

Figure 3. Forest plot diagram showing the effect of TXA on intra-operative blood loss. The black diamond signifies that the mean difference is in favour of TXA. The size of each square depends on the weight of each study. A green square is given to continuous outcomes.

**Intra-Op Blood Loss: -128mL (33.82-222.73mL)**

Yang et al; PLoS One 2013
### Post-Op Blood Loss

<table>
<thead>
<tr>
<th>TXA Group Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>TXA Group Control Group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 blood loss (Post-operative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elwood2008</td>
<td>215.31</td>
<td>32</td>
<td>276.04</td>
<td>215.31</td>
<td>32</td>
<td>276.04</td>
<td>32</td>
<td>2.1%</td>
<td>-117.37 [-224.03, -10.71]</td>
<td>170</td>
</tr>
<tr>
<td>Park2000</td>
<td>345.5</td>
<td>34</td>
<td>42.16</td>
<td>345.5</td>
<td>34</td>
<td>42.16</td>
<td>34</td>
<td>8.0%</td>
<td>-116.70 [-139.22, -94.18]</td>
<td>170</td>
</tr>
<tr>
<td>Tsushimamoto2011</td>
<td>211</td>
<td>20</td>
<td>211.5</td>
<td>211</td>
<td>20</td>
<td>211.5</td>
<td>20</td>
<td>32.2%</td>
<td>-79.00 [-105.92, -52.08]</td>
<td>170</td>
</tr>
<tr>
<td>Wong2005</td>
<td>73</td>
<td>73</td>
<td>524</td>
<td>73</td>
<td>73</td>
<td>524</td>
<td>74</td>
<td>0.9%</td>
<td>-201.00 [-362.02, -39.98]</td>
<td>170</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>170</td>
<td></td>
<td></td>
<td>171</td>
<td>100.0%</td>
<td>-98.49 [-113.77, -83.22]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CH² = 7.22; df = 4 (P = 0.12); I² = 45%</td>
<td>Test for overall effect: Z = 12.64 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>170</td>
<td></td>
<td></td>
<td>171</td>
<td>100.0%</td>
<td>-98.49 [-113.77, -83.22]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CH² = 7.22; df = 4 (P = 0.12); I² = 45%</td>
<td>Test for overall effect: Z = 12.64 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Figure 4. Forest plot diagram showing the effect of TXA on post-operative blood loss. The black diamond signifies that the mean difference is in favour of TXA. The size of each square depends on the weight of each study. A green square is given to continuous outcomes.

**Post-Op Blood Loss: -98.49mL (83.22-113.77mL)**

1 Yang et al; PLoS One 2013

### Systematic Review and Meta-Analysis of Perioperative Intravenous Tranexamic Acid Use in Spinal Surgery

#### Total Blood Loss

<table>
<thead>
<tr>
<th>TXA Group Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>TXA Group Control Group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 blood loss (total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong2005</td>
<td>3.079</td>
<td>2.559</td>
<td>73</td>
<td>3.563</td>
<td>3.030</td>
<td>74</td>
<td>4.4%</td>
<td>-1264.00 [-2190.05, -377.95]</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Sethna2005</td>
<td>2.120</td>
<td>0.523</td>
<td>23</td>
<td>2.085</td>
<td>1.169</td>
<td>21</td>
<td>1.7%</td>
<td>-506.50 [-763.92, -249.08]</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Park2000</td>
<td>0.661</td>
<td>0.597</td>
<td>20</td>
<td>0.646</td>
<td>0.570</td>
<td>20</td>
<td>34.7%</td>
<td>-139.00 [-214.73, -63.27]</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Tsushimamoto2011</td>
<td>205.9</td>
<td>20</td>
<td>205.9</td>
<td>205.9</td>
<td>20</td>
<td>205.9</td>
<td>20</td>
<td>21.9%</td>
<td>-89.69 [-132.15, -47.45]</td>
<td>199</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>199</td>
<td></td>
<td></td>
<td>198</td>
<td>100.0%</td>
<td>-389.21 [-440.66, -177.83]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 52919.50; CH² = 33.12; df = 6 (P &lt; 0.00001); I² = 82%</td>
<td>Test for overall effect: Z = 3.61 (P &lt; 0.00003)</td>
<td></td>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>199</td>
<td></td>
<td></td>
<td>198</td>
<td>100.0%</td>
<td>-389.21 [-440.66, -177.83]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 52919.50; CH² = 33.12; df = 6 (P &lt; 0.00001); I² = 82%</td>
<td>Test for overall effect: Z = 3.61 (P &lt; 0.00003)</td>
<td></td>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Figure 5. Forest plot diagram showing the effect of TXA on total blood loss. The black diamond signifies that the mean difference is in favour of TXA. The size of each square depends on the weight of each study. A green square is given to continuous outcomes.

**Total Blood Loss: -389.21mL (177.83-600.60mL)**

1 Yang et al; PLoS One 2013
Blood Transfusion Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TAX Group</th>
<th></th>
<th>Control Group</th>
<th></th>
<th>Risk Ratio</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H. Fixed, 95% CI</td>
<td>M-H. Fixed, 95% CI</td>
</tr>
<tr>
<td>4.1.1 Blood transfusion rate</td>
<td>4</td>
<td>32</td>
<td>12</td>
<td>32</td>
<td>9.8%</td>
<td>0.33 [0.12, 0.92]</td>
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</tr>
<tr>
<td>Elwatidy2008</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>38</td>
<td>15</td>
<td>12.3%</td>
<td>0.67 [0.34, 1.29]</td>
</tr>
<tr>
<td>Farrokh2011</td>
<td>16</td>
<td>34</td>
<td>28</td>
<td>34</td>
<td>22.9%</td>
<td>0.57 [0.39, 0.84]</td>
<td></td>
</tr>
<tr>
<td>Hang C2011</td>
<td>2</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>3.3%</td>
<td>0.50 [0.11, 2.19]</td>
<td></td>
</tr>
<tr>
<td>kim 2000</td>
<td>66</td>
<td>122</td>
<td>97</td>
<td>122</td>
<td>21.4%</td>
<td>0.85 [0.56, 1.30]</td>
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<tr>
<td>Neillipovitz 2001</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>12</td>
<td>26.5%</td>
<td>0.57 [0.39, 0.84]</td>
<td></td>
</tr>
<tr>
<td>Sethna 2005</td>
<td>23</td>
<td>73</td>
<td>30</td>
<td>74</td>
<td>27.6%</td>
<td>0.78 [0.50, 1.20]</td>
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</tr>
<tr>
<td>Wong 2005</td>
<td>222</td>
<td>222</td>
<td>222</td>
<td>222</td>
<td>100.0%</td>
<td>0.65 [0.53, 0.80]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>233</td>
<td>228</td>
<td>100.0%</td>
<td>0.65 [0.53, 0.80]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>233</td>
<td>228</td>
<td>100.0%</td>
<td>0.65 [0.53, 0.80]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rate of allogeneic blood transfusion ↓ by a relative 35%

Yang et al; PLoS One 2013

Systematic Review and Meta-Analysis of Perioperative Intravenous Tranexamic Acid Use in Spinal Surgery

TXA & DVT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TAX Group</th>
<th></th>
<th>Control Group</th>
<th></th>
<th>Risk Ratio</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H. Fixed, 95% CI</td>
<td>M-H. Fixed, 95% CI</td>
</tr>
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<td>5.1.1 DVT</td>
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<td>32</td>
<td>Not estimable</td>
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</tr>
<tr>
<td>Elwatidy2008</td>
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<td>4</td>
<td>0</td>
<td>4</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farrokh2011</td>
<td>16</td>
<td>34</td>
<td>0</td>
<td>34</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hang C2011</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neillipovitz 2001</td>
<td>66</td>
<td>122</td>
<td>0</td>
<td>122</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sethna 2005</td>
<td>23</td>
<td>73</td>
<td>0</td>
<td>73</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong 2005</td>
<td>222</td>
<td>222</td>
<td>0</td>
<td>222</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>242</td>
<td>237</td>
<td>100.0%</td>
<td>0.34 [0.01, 8.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>242</td>
<td>237</td>
<td>100.0%</td>
<td>0.34 [0.01, 8.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No statistical difference

Yang et al; PLoS One 2013
Dosing Regimen for TXA

**Loading Dose:**
10-15mg/kg over 10min
(80% inhibition of fibrinolytic process in tissues)

**Maintenance Dose Options:**
a. 1g every 8hrs
b. 1-2mg/kg/hr. till skin closure

Zhang et al; World Neurosurg 2019
Shakur et al; Lancet 2010
Yang et al; PLoS One 2013
McCormack et al; Drugs 2012
Summary

Peri-op TXA significantly reduces blood loss and transfusion rates

Recommended doses 10-15mg/kg loading dose followed by continuous infusion @ 1-2mg/kg/hr

No Major Complications or Adverse Effects

Exercise caution in patients who are at higher risk of DVT/PE (h/o PE or DVT, Coronary stents, Malignancies etc.,)

Outline

• Preoperative Fasting and Carbohydrate Loading

• Use of Tranexamic Acid in Spine Surgery

• Role of Methadone & Regional Blocks in Multi-modal Analgesia
Peri-Operative Analgesia in Spine Surgery

Incidence of chronic opioid intake after spine surgery in opioid naïve patients 18.3% 

Dunn et al; Anesth Analg. 2018  
Sandkuhler J et al; Lancet 2002  
Trafton et al; J Neurosci 2000  
Borgland et al; Clin Exp Pharmacol Physiol 2001

Multimodal Analgesia for Spine Surgery

Pre emptive analgesia
- NSAIDs
- Gabapentin  
- Pregabalin  
- Acetaminophen

Perioperative intravenous adjuvants
- NMDA antagonists
- Ketamine
- Methadone
- Magnesium
- Lidocaine
- Dexmedetomidine
- Naloxone

Neuraxial blockade
- Epidural Analgesia
- Intrathecal
- Caudal Analgesia

Regional nerve blocks
- Low thoracic erector spine
- Multifidus cervicis plane
- Intersemissinal plane (ISP)
- Thoracolumbar interfascial plane (TLIP)

Rajan et al; J Neurosurg Anesthesiol 2020
Methadone

- Long-acting opioid agonist
- Stable blood conc. with single intra-op IV dose
- Medication assisted treatment of opioid abuse disorder
- High Oral Bioavailability

Kharasch et al; Anesth Analg 2011
Gagnon et al; Pain Res Manag 2003
Gourlay et al; Anesthesiology 1984
Mattick et al; Cochrane Database Syst Rev 2009

\[ \mu, \delta \]
- Potent agonist
- Potent analgesia (longer acting)

NMDA
- Potent antagonist
- Counteract tolerance, hyperalgesia, chronic post surgical pain

5-HT, NE
- Inhibit reuptake of neurotransmitters
- Antinociception, mood elevation

Kharasch et al; Anesth Analg 2011
Gagnon et al; Pain Res Manag 2003
Gourlay et al; Anesthesiology 1984
**Methadone Dosing**

1. **Intra-Operative Dosing (Duration Dose Dependent)**
2. **Smaller Doses: (5-10mg) Short acting opioid (3-4hrs)**
3. **Higher Dose (20mg+): Elimination ½ life parallels clinical effect (approx. 35hrs)**
4. **Target Dosing in Excess of Minimal Analgesic Concentration**
5. **Dose: 0.2mg/kg intravenous**
6. **Long Elimination ½ Life (24-36hrs.)**

**Table 1. Onset of Effect and Elimination of Opioids**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>$t_{1/2}$</th>
<th>$K_{e,r}$</th>
<th>Elimination $t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>1 minute</td>
<td>0.5 hour</td>
<td></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>1 minute</td>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>6 minutes</td>
<td>8 hours</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5 minutes</td>
<td>8-10 hours</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>2-4 hours</td>
<td>2-3 hours</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>8 minutes</td>
<td>24-36 hours</td>
<td></td>
</tr>
</tbody>
</table>

Kharasch et al; Anesth Analg 2011
Gagnon et al; Pain Res Manag 2003
Gourlay et al; Anesthesiology 1984

**Pharmacokinetic Model- Methadone**

Kharaasch et al; Anesth Analg 2011
Methadone in Spine Surgery

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Total Design</th>
<th>Total</th>
<th>Type of Surgery</th>
<th>Intraoperative Opioid Used in the Control Group</th>
<th>Intraoperative Opioid Used in the Methadone Group</th>
<th>Postoperative Analgesic Requirements</th>
<th>Postoperative VAS Pain Scores are on a 0-10 Scale</th>
<th>Other Findings</th>
<th>Postoperative Complications</th>
<th>Limitations of the Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safford et al. 2011</td>
<td>Randomized, double-blind</td>
<td>20</td>
<td>Complex spine surgery</td>
<td>15 x 0.2 mg at 30 min of surgery</td>
<td>15 x 0.2 mg of 4% lidocaine at 0 min of surgery</td>
<td>None</td>
<td>Prevalence of back pain significantly reduced compared to the control group</td>
<td>No differences between groups</td>
<td>No differences between groups</td>
<td>Small sample size, small number of patients</td>
</tr>
<tr>
<td>Murphy et al. 2017</td>
<td>Randomized, double-blind</td>
<td>120</td>
<td>Complex spine surgery</td>
<td>0.2 mg/kg/h of methadone</td>
<td>0.2 mg/kg/h of methadone</td>
<td>None</td>
<td>No differences in VAS pain scores compared to the control group</td>
<td>No differences between groups</td>
<td>No differences between groups</td>
<td>Patient selection bias</td>
</tr>
</tbody>
</table>
| Stevens et al. 2011 | Open-label protocol | 82 | Complex spine surgery, adolescents | 6.1 ± 1.0 mg/kg | 6.1 ± 1.0 mg/kg | 0.5 ± 0.1 mg/kg | No significant difference between groups | No significant difference between groups | No significant difference between groups | Small sample size, uncontrolled pain |}

| Shohat et al. 2013 | Observational, prospective study | 30 | Complex spine surgery, adolescents | 0.225-0.25 mg/kg at induction of anesthesia | 0.225-0.25 mg/kg at induction of anesthesia | 0.225-0.25 mg/kg at induction of anesthesia | No differences between groups | No differences between groups | No differences between groups | Small sample size, uncontrolled pain |

Table 1. Postoperative Analgesic Requirements in the Investigation by Murphy et al. 18

<table>
<thead>
<tr>
<th>Group</th>
<th>Hydromorphone, mg</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU</td>
<td>1 (0.5 to 1.5)</td>
<td>-0.6 (-1.1 to -0.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>First 24 h</td>
<td>4.56 (2.3 to 7.1)</td>
<td>-4.8 (-6.9 to -2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Second 24 h</td>
<td>0.60 (0.71 to 2.8)</td>
<td>-2.9 (-8.9 to -0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third 24 h</td>
<td>0 (0 to 0.05)</td>
<td>-0.125 (-0.6 to 0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>5.05 (3.1 to 8.9)</td>
<td>-12.2 (-12.1 to -4.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The data are reported as medians (interquartile range) and were compared between groups at the various times using the Mann-Whitney U test. No within-group (i.e., across time) comparisons have been made. The oral pain tablets contained 10 mg of hydromorphone with 32.5 mg of acetaminophen. n = 62 in the methadone group, and n = 53 in the hydromorphone group, except where indicated. Reprinted with permission from Murphy et al. 18

*P < 0.05

Murphy et al: Anesthesiology 2017
Limitations of Methadone Clinical Trials

- Few studies with potential analgesic benefits of methadone in conjunction with other opioid-sparing agents
- Overestimate magnitude of association
- Small numbers in clinical studies
- False positives

Safety of Methadone

- Adverse Respiratory Events
- Does not appear to increase the risk of other opioid-related side effects
- Post-Op Sedation
- PONV
- Cardiac Events
- Bowel Movements

References:
Murphy et al; Anesthesiology 2017
Murphy et al; Anesthesiology 2015
Chui et al; Anaesth Intensive Care 1992
Questions in Future Studies

- Optimal dose for various surgical procedures?
- Safety of methadone in high-risk population?
- QTc prolongation and cardiac arrhythmias?
- Reduce risk of development of postsurgical pain?
- Role in ERAS Spine protocols?

ESPB in Spine Surgery

Chin et al; Spine 2018

Nagele et al; Anesthesiology 2012
ESPB in Spine Surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Size</th>
<th>Surgical Operation</th>
<th>ESPB</th>
<th>Outcome</th>
<th>Side Effect</th>
<th>Follow-Up Time</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al (2019)</td>
<td>India</td>
<td>RCT</td>
<td>40</td>
<td>Lumber spinal surgery</td>
<td>T10 vertebra level, both sides with 20 ml, bupivacaine 0.5%, single-shot.</td>
<td>Opioid consumption, NRS scores, patient satisfaction.</td>
<td>Two patients in the control group developed severe nausea and vomiting</td>
<td>24 hours</td>
<td>US-guided ESP block reduces postoperative opioid requirement and improves patient satisfaction.</td>
</tr>
<tr>
<td>Usho et al (2019)</td>
<td>Japan</td>
<td>Retrospective study</td>
<td>61</td>
<td>Lumbar spinal surgery</td>
<td>Target vertebral level, both sides with 20 mL levobupivacaine 0.375%.</td>
<td>NRS scores, analgesia consumption, complications.</td>
<td>None</td>
<td>24 hours</td>
<td>The ESP block provides effective postoperative analgesic effect for 24 hours.</td>
</tr>
<tr>
<td>Yark et al (2019)</td>
<td>Turkey</td>
<td>RCT</td>
<td>60</td>
<td>Open lumbar decompression</td>
<td>L3 vertebra level, both sides with 20 mL, bupivacaine 0.25%, single-shot.</td>
<td>VAS scores, opioid consumption, rescue analgesia, opioid-related side effects.</td>
<td>None</td>
<td>24 hours</td>
<td>ESP block can be used in multimodal analgesia practice to reduce opioid consumption and relieve acute postoperative pain.</td>
</tr>
</tbody>
</table>

Qiu et al; JPR 2020

Erector Spinae Plane Block

- Novel, safe, and simple technique
- Block transmission of pain signals through dorsal rami of spinal nerves
- The site of injection superficial to the tips of the transverse processes
- Limitations:
  - Paraspinal, Epidural spread
  - Lack of large studies
Field Block with Adjuvants

### Summary: Methadone & Regional Blocks

- **Methadone**
  - Long acting opioid agonist
  - Single dose of 0.2mg/kg at induction may provide analgesia for up to 30+hrs & reduce post-op opioid requirements by 30-50%
  - Large RCTs to study dosing and efficacy of methadone

- **Regional Blocks**
  - Regional blocks- Analgesic effect by blocking dorsal rami of spinal nerves
  - Opioid sparing effect in peri-op and post-op period
  - Drawbacks
    - Paraspinal, Epidural spread
    - Specialist skillset for ESP
    - Lack of large RCT

---

**TABLE 3.** Mean Value (Standard Deviation) of AUC of Pain Expressed in Pain Unit × Hour and of Rescue Morphine Consumption (Given Subcutaneously) in Milligram for Control and Clonidine Groups, for Each Surgical Subgroup and for all Surgical Subgroups Taken Together

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Spinal fusion</th>
<th>Lumbar stenosis</th>
<th>Cervical stenosis</th>
<th>Microdiscectomy</th>
<th>All surgical subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome parameter</td>
<td>Mean (n = 42)</td>
<td>Mean (n = 38)</td>
<td>Mean (n = 14)</td>
<td>Mean (n = 15)</td>
<td>Mean (n = 45)</td>
</tr>
<tr>
<td>Total AUC</td>
<td>694 (294)</td>
<td>566 (198)</td>
<td>&lt;.005</td>
<td>673 (285)</td>
<td>430 (220)</td>
</tr>
<tr>
<td>Total rescue morphine</td>
<td>16.8 (1.6)</td>
<td>7.0 (1.1)</td>
<td>&lt;.001</td>
<td>16.5 (1.7)</td>
<td>4.3 (5.7)</td>
</tr>
</tbody>
</table>

Hay et al: Neurosurg 2018
Summary

CHO loading is safe & improves subjective well-being
ERAS strongly recommends its use for elective procedures

TXA is an essential drug in spine surgery
Significant reduction in blood loss & transfusion requirements with TXA

Multimodal analgesia with methadone +/- regional/field blocks may reduce use of opioids in post-op period

• Q&A button:

• Raise Hand button: