Adjuvants for peripheral nerve blocks

Daan Bringmans
Why adjuvants in peripheral nerve blocks?

- increase speed of onset
- increase duration of action
- increase density or quality of block
- decrease toxicity of local anesthetic
Risk with adjuvants?

- neurotoxicity
- local irritation
- systemic side effects
  - nausea, vomiting
  - brady- or tachycardia, hypo- or hypertension, ...
  - ...
- not soluble with LA
- costly
- dosage failure
Catheters?

• Why not?
  – specialized training
  – catheter migration
  – anaesthetic leakage
  – infection
  – hemorrhage
  – LA toxicity secondary to intravascular placement
  – pump malfunction
  – requiring complex logistic organisation
  – placement more time consuming and painful
  – higher risk with out of hospital use
What’s been tried?

- Epinephrine
- Sodium bicarbonate
- $\alpha_2$-agonists (clonidine, dexmedetomidine)
- Opioids (fentanyl, sufentanil, morphine, buprenorphine, nalbuphine, tramadol)
- Steroids (dexamethasone, methylprednisolone)
- Midazolam

- Neostigmine
- Verapamil
- Magnesium
- Ketamine
- NSAIDS (Ketorolac)
- Lysine acetylsalicylate
- Many others …
BUT do they work ???
Epinephrine

• Mechanism:
  – vasoconstriction $\alpha_1$-activation
  – reduction of bloodflow
  – decreasing clearance of LA $\rightarrow$ prolonging exposure of the nerve to LA

• Studies: yes but
  – lidocaine: 70% longer duration (25-40min)
  – bupivacaine or ropivacaine: max 20% longer duration

• Other benefits:
  – decrease systemic toxicity: 30-50% lower plasma levels LA $\rightarrow$
    higher acceptable max dose LA
  – “intravascular marker”
## Epinephrine

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogru et al.</td>
<td>Lidocaine 1.5%[^42]</td>
<td>Axillary-200mcg/ml</td>
<td>45min**</td>
<td>Tachycardia and hypertension with 200mcg</td>
<td>No</td>
<td>IV</td>
</tr>
<tr>
<td>Song et al.</td>
<td>Mepivacaine 1%[^43]</td>
<td>Brachial plexus-200mcg</td>
<td>1h***</td>
<td>None</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Weber et al.</td>
<td>Ropivacaine 0.5% and 0.2%[^44]</td>
<td>Femoral-5mcg/ml</td>
<td>None*</td>
<td>None</td>
<td>No</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.
Epinephrine

- **Dose:**
  - 1:200.000 (5mcg/ml) commonly used neuraxial
  - lower doses recommended for PNB 1:400.000 or 2,5mcg/ml
  - equally vasoactive at LA concentrations of 0.125% compared with those as high as 0.75%

- **Concerns:**
  - systemic reaction (tachycardia, hypertension, anxiety, etc)
  - compromise endoneural blood flow & increase neurotoxicity
    - limited evidence: reduction of blood flow may be significant, but only transiently
    - some patients more susceptible to injury (diabetic, smoking, hypertension, …)
Epinephrine

- **Recommendations:**
  - not recommended for general use
  - limited benefit in prolongation of block (45-60min)
  - intravascular injection: caution for hypertension and tachycardia
  - high doses can result in systemic absorption
  - population at risk: higher risk for neurotoxicity
Clonidine

- One of the most widely used additives
- Mechanism:
  - α2-agonist with local vasoconstrictor properties
  - direct action on peripheral nerves: hyperpolarization of cyclic-nucleotide-gated cation channels
  - affects C fibers (pain) >>>> Aα-fibers (motor)
  - dose: 0.5mcg/kg and max 150mcg
- Side effects (more common with dose > 100 mcg):
  - bradycardia, hypotension, sedation and fainting.
## Clonidine

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YaDeau JT et al</td>
<td>Bupivacaine 0.375% [53]</td>
<td>Sciatic popliteal-100mcg</td>
<td>~3-4h**</td>
<td>None</td>
<td>Yes (IM)</td>
<td>V</td>
</tr>
<tr>
<td>Fournier R et al</td>
<td>Levobupivacaine 0.5% [54]</td>
<td>Sciatic popliteal-150mcg</td>
<td>None*</td>
<td>50% with clonidine experience. &gt;20% decrease in systolic BP</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Jaiswal R et al</td>
<td>Ropivacaine 0.5% [55]</td>
<td>Axillary-150mcg</td>
<td>None***</td>
<td>None</td>
<td>No</td>
<td>IV+</td>
</tr>
<tr>
<td>Kohli S et al</td>
<td>Bupivacaine 0.5% [56]</td>
<td>SCB-1 mcg/kg vs. 2 mcg/kg</td>
<td>21h with 2mcg/kg, 15h with 1mcg/kg</td>
<td>Higher hypotension, bradycardia, and sedation in 2mcg/kg group</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Chakraborty S</td>
<td>Bupivacaine 0.5% [57]</td>
<td>SCB-30mcg</td>
<td>220min*</td>
<td>Sedation</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Molnar RR et al</td>
<td>Lidocaine 1.5% (note: comparison to epinephrine 5mcg/ml) [58]</td>
<td>Cervical plexus-5mcg/ml</td>
<td>None**</td>
<td>Increased lidocaine plasma concentrations compared to epinephrine</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Trivedi V et al</td>
<td>Bupivacaine 0.5% and lidocaine 2% (note: comparison to 5mg midazolam) [59]</td>
<td>SCB-150mcg</td>
<td>None**</td>
<td>None</td>
<td>No</td>
<td>I+</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.

Kirksey, M.A. et al., 2015. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: A systematic qualitative review. PLoS ONE.
Clonidine

• Literature:
  – conflicting evidence
    • Zero effect to faster onset and longer duration
  – not clear which LA, blocks or doses of clonidine are optimal for prolongation of analgesia after peripheral nerve blocks
  – meta-analysis of 20 papers shows ± 2h prolongation
  – high doses (2mcg/kg) result in systemic side effects (hypotension, sedation and bradycardia)
Dexmedetomidine

• Mechanism:
  – α2-agonist: 7 times higher affinity for α2-receptor than clonidine
  – blocking of the hyperpolarization-activated cation current

• Adverse events
  – reversible bradycardia less than 10%, no clinically significant hypotension
  – neurotoxicity: limited data, potentially neuroprotective when combined with lidocaine and bupivacaine
  – cardiotoxicity: may attenuate cardiotoxicity of bupivacaine
# Dexmedetomidine

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal S et al</td>
<td>Bupivacaine 0.375%[^64]</td>
<td>SCB- 100mcg</td>
<td>~8h*</td>
<td>Bradycardia in one patient</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Fritsch G et al</td>
<td>Ropivacaine 0.5%[^65]</td>
<td>ISB- 150mcg</td>
<td>~4h**</td>
<td>Lower HR with dexmedetomidine, no neurotoxicity</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Lin YN et al</td>
<td>Ropivacaine 0.375%[^66]</td>
<td>Cervical plexus- 1mcg/kg</td>
<td>~50min**</td>
<td>Sedation, bradycardia requiring atropine</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Song JH et al</td>
<td>Mepivacaine 1%[^43]</td>
<td>Brachial plexus- 1mcg/kg</td>
<td>~75min**</td>
<td>Bradycardia</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Marhofer D et al</td>
<td>Ropivacaine 0.75%[^67]</td>
<td>Ulnar nerve block- 20mcg</td>
<td>~200min***</td>
<td>None</td>
<td>Yes (IV)</td>
<td>IV</td>
</tr>
<tr>
<td>Rancourt MP et al</td>
<td>Ropivacaine 0.5%[^68]</td>
<td>Posterior tibial- 1mcg/kg</td>
<td>~4.5h**</td>
<td>Hypotension, bradycardia</td>
<td>No</td>
<td>V</td>
</tr>
</tbody>
</table>

[^64]: Kirksey, M.A. et al., 2015. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: A systematic qualitative review. *PLoS ONE.*
Dexmedetomidine

- Review: mean increased duration time of 284 minutes
- Recommendations
  - dose 1mcg/kg
  - Use in patients where bradycardia and hypotension are likely to be treatable with conventional therapy
  - useful with levobupivacaine, ropivacaine and bupivacaine
Opioids

- Use of traditional opioids is poorly supported by the literature
- Peripheral opioid receptors led to the clinical application of adding opioids to LA
- Opioids
  - buprenorphine (Temgesic)
  - fentanyl
  - tramadol
Buprenorphine

• **Mechanism:**
  - highly lipophilic partial opioid receptor agonist
  - LA-like capacity to block voltage gated Na+ channels
  - K-antagonist, ORL-1 and δ-agonist in addition to µ-agonist
    → antihyperalgesic effects

• **Side effects:**
  - no reported (significant) increase in side effects or clinical toxicity
  - higher risk of postoperative nausea and vomiting
  - but exposure for 24 hours results in significant cell death in rats
## Buprenorphine

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candido KD et al</td>
<td>Bupivacaine 0.5% + epi [18]</td>
<td>Sciatic—0.3mg</td>
<td>6h*</td>
<td>PONV events: 7 in control group, 21 in IM buprenorphine group, 19 in PN buprenorphine group</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Candido KD et al</td>
<td>Mepivacaine 1% + tetracaine 0.02% + epi [16]</td>
<td>Axillary—0.3mg</td>
<td>15h**</td>
<td>None</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Candido KD et al</td>
<td>Mepivacaine 1% + tetracaine 0.02% + epi [17]</td>
<td>SCB—0.3mg</td>
<td>12h?</td>
<td>PONV in 2/20 in PN buprenorphine group, 6/20 in IM buprenorphine group, and 3/20 in control group</td>
<td>Yes</td>
<td>V</td>
</tr>
<tr>
<td>Behr A et al</td>
<td>Levobupivacaine 0.75% [19]</td>
<td>ISB—0.15mg</td>
<td>6h***</td>
<td>PONV in 4/50 pts; hypotension in 1/50 pts</td>
<td>No</td>
<td>IV+</td>
</tr>
<tr>
<td>Bazin JE et al</td>
<td>Lidocaine 1% + bupivacaine 0.5% [15]</td>
<td>SCB- 3mcg/kg</td>
<td>9h*</td>
<td>Pruritus in 4/20 pts; PONV in 10/20 pts</td>
<td>No</td>
<td>II</td>
</tr>
<tr>
<td>Jadon A et al</td>
<td>Bupivacaine 0.3% [20]</td>
<td>SCB- 3mcg/kg</td>
<td>6h**</td>
<td>PONV in 2/20 pts in PN buprenorphine group and 2/20 pts in IM buprenorphine group. No buprenorphine-free control group.</td>
<td>Yes (IM)</td>
<td>III</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.
Buprenorphine

• **Recommendation:**
  - consistently shown to prolong peripheral nerve blocks
  - only with multimodal nausea prophylaxis
  - avoiding use in patients with a history of PONV

• **Dose:** 0.3mg with LA
Fentanyl

- Literature:
  - little benefit: 1h prolongation
  - multiple other papers have failed to show a benefit

- Adverse effects:
  - small increases in rates of sedation, bradycardia, and hypercapnia
## Fentanyl

<table>
<thead>
<tr>
<th>Agent</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sert H et al</td>
<td>Articaine 2%</td>
<td>Axillary-100mcg</td>
<td>2h*, 1h***</td>
<td>5/22 with sedation in fentanyl group, 2/22 with sedation in control group.</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Bhuvaneswari V</td>
<td>Bupivacaine 0.25% + epi[37]</td>
<td>Paravertebral—0.6mcg/kg</td>
<td>12h*</td>
<td>None</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Sindjelic RP et al</td>
<td>Bupivacaine 0.5% + lidocaine 2%[38]</td>
<td>Cervical plexus-50mcg</td>
<td>3h*</td>
<td>Bradycardia in 2/38 in fentanyl group, 1/38 in control group. Hypercapnia in 3/38 in fentanyl group, 1/38 in control group.</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Fanelli G et al</td>
<td>Ropivacaine 0.75%[39]</td>
<td>Axillary-20mcg</td>
<td>None</td>
<td>Not reported</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Nishikawa K et al</td>
<td>Lidocaine 1.5% + epi[38]</td>
<td>Axillary-100mcg</td>
<td>None</td>
<td>Not reported</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Fletcher D et al</td>
<td>Lidocaine 1.5% + epi[31]</td>
<td>Axillary-100mcg</td>
<td>1h**,***</td>
<td>Not reported</td>
<td>Yes (IV)</td>
<td>V</td>
</tr>
<tr>
<td>Magistris L et al</td>
<td>Ropivacaine 0.75%[33]</td>
<td>Sciatic/femoral-1mcg/kg</td>
<td>None</td>
<td>No difference in sedation or oxygen saturation</td>
<td>No</td>
<td>IV+</td>
</tr>
<tr>
<td>Kardash K et al</td>
<td>Mepivacaine 1.5% + epi [32]</td>
<td>SCB- 75mcg</td>
<td>1h**</td>
<td>Not reported</td>
<td>Yes (IM)</td>
<td>III</td>
</tr>
<tr>
<td>Moharari R et al</td>
<td>Lidocaine 1.5%[34]</td>
<td>ISB-75mcg</td>
<td>None</td>
<td>Not reported</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Karakaya D et al</td>
<td>Bupivacaine 0.25%[35]</td>
<td>Axillary-100mcg</td>
<td>3h***, 10h**</td>
<td>Nausea in 1/20 pts in each fentanyl group, 0/20 in control group. No sedation in any group.</td>
<td>No</td>
<td>III+</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.
Tramadol

• Mechanism:
  – weak central-acting opioid, little effect on µ-receptor and κ-receptor
  – Na+ and K+ channel blocking properties
  – block motor and nociceptive function similarly to LA

• Literature:
  – conflicting data: largely negative, especially when combined with long-acting local anesthetics and when systemic control groups are included.
  – not recommended as a adjuvant with LA
<table>
<thead>
<tr>
<th>Agent</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemanno F et al</td>
<td>Levobupivacaine 0.5% [89]</td>
<td>ISB—1.5mg/kg</td>
<td>7h*</td>
<td>None</td>
<td>Yes (IM)</td>
<td>V</td>
</tr>
<tr>
<td>Kaabachi O et al</td>
<td>Lidocaine 1.5% + epi[90]</td>
<td>Axillary- 200mg</td>
<td>160min*, 65min***</td>
<td>None</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Sarsu S et al</td>
<td>Levobupivacaine 0.5% + lidocaine 2%[91]</td>
<td>Axillary- 100mg</td>
<td>None*</td>
<td>Sedation, nausea</td>
<td>No</td>
<td>IV+</td>
</tr>
<tr>
<td>Mannion S et al</td>
<td>Levobupivacaine 0.5% [92]</td>
<td>Psoas—1.5mg/kg</td>
<td>None*</td>
<td>None</td>
<td>Yes (IV)</td>
<td>V</td>
</tr>
<tr>
<td>Robaux S et al</td>
<td>Mepivacaine 1.5%[93]</td>
<td>Axillary- 40mg, 100mg, 200mg</td>
<td>60min, 40min, 40min*</td>
<td>Nausea/vomiting</td>
<td>No</td>
<td>IV</td>
</tr>
<tr>
<td>Kapral S et al</td>
<td>Mepivacaine 1%[94]</td>
<td>Axillary- 100mg</td>
<td>100min***</td>
<td>None</td>
<td>Yes (IV)</td>
<td>IV</td>
</tr>
<tr>
<td>Kesimci E et al</td>
<td>Ropivacaine 0.75%[95]</td>
<td>Axillary- 100mg</td>
<td>None*</td>
<td>None</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Omar AM et al</td>
<td>Bupivacaine 0.5%[96]</td>
<td>Paravertebral—1.5mg/kg</td>
<td>None*</td>
<td>None</td>
<td>No</td>
<td>V</td>
</tr>
</tbody>
</table>

*Time to first analgesic; **Time to first reported pain; ***Time to pinprick or restoration of sensation.

Kirksey, M.A. et al., 2015. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: A systematic qualitative review. PLoS ONE.
Dexamethasone

- **Mechanism:**
  - high-potency, long-acting glucocorticoid with little mineralocorticoid effect
  - decreased nociceptive C-fibre activity through a direct effect on glucocorticoid receptors and inhibition of potassium channels
  - systemic anti-inflammatory effect

- **Literature:**
  - increased duration by 233 (172–295) min when injected with short- or medium-term action LA and by 488 (419–557) min when injected with long-term action LA
  - no differences between 4 and 8 mg dexamethasone
  - less PONV
# Dexamethasone

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fredrickson MJ</td>
<td>Bupivacaine 0.5%[77]</td>
<td>Sciatic/saph-8mg; ankle-8mg</td>
<td>Sciatic/saph—13% of patients with pain in first 24hrs vs. 47% in IM group; ankle—none</td>
<td>Not reported</td>
<td>Yes (IM)</td>
<td>V</td>
</tr>
<tr>
<td>Desmet M et al</td>
<td>Ropivacaine 0.5%[76]</td>
<td>ISB- 10mg</td>
<td>None</td>
<td>3.8- and 5.1-mg/dL increase in blood glucose with PN and IV administration</td>
<td>Yes (IV)</td>
<td>V</td>
</tr>
<tr>
<td>Rahangdale R et al</td>
<td>Bupivacaine 0.5% + epi[79]</td>
<td>Sciatic- 8mg</td>
<td>None</td>
<td>Statistically insignificant increase in incidence of numbness and paresthesia at 24 and 48hrs. No symptoms persisted at 8wks in any group.</td>
<td>Yes (IV)</td>
<td>V</td>
</tr>
<tr>
<td>Ammar AS et al</td>
<td>Bupivacaine 0.25%[74]</td>
<td>TAP- 8mg</td>
<td>1h*</td>
<td>Decreased nausea and vomiting (6/30 with dexamethasone vs. 14/30 with control).</td>
<td>No</td>
<td>IV+</td>
</tr>
<tr>
<td>Liu J et al</td>
<td>Bupivacaine 0.25%[81]</td>
<td>SCB- 1mg, 2mg, 4mg</td>
<td>10h*</td>
<td>One transient paresthesia noted in 2mg group</td>
<td>Yes (IV)</td>
<td>V</td>
</tr>
<tr>
<td>Biradar PA et al</td>
<td>Lidocaine 1.5% + epi[73]</td>
<td>SCB- 8mg</td>
<td>3h**</td>
<td>None</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Saritas A et al</td>
<td>Prilocaine 2%[76]</td>
<td>Axillary- 8mg</td>
<td>3h**</td>
<td>Not reported</td>
<td>No</td>
<td>IV+</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.

Kirksey, M.A. et al., 2015. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: A systematic qualitative review. *PLoS ONE.*
Dexamethasone

• Perineural vs intravenous?
  – IV equivalent to perineural dexamethasone in prolonging the analgesic duration of a single-shot ISB
  – dexamethasone is not licensed for perineural use → IV use

Sodium bicarbonate

• Mechanism:
  – alkalinization of LA, more non ionized form of LA
  – less injection pain, faster onset
  – useful lidocaine, mepivacaine but can cause precipitation when mixed with bupivacaine and ropivacaine

• Studies:
  – difference of 1 or 2 minutes may not be significant in a clinical setting
  – some evidence: also shortens duration of action by about 50% ???

• Recommendation:
  – no clinical benefit
Midazolam

• Mechanism:
  – water-soluble benzodiazepine
  – indirect gamma-aminobutyric acid receptor agonist
  – studies: adjuvant for neuraxial anesthesia
  – very limited data on efficacy for PNB: 2 known studies, both show improved analgesia when added to bupivacaine brachial plexus blocks

• Conclusion:
  – intrathecal midazolam has been shown to be neurotoxic
  – should be avoided as a perineural adjuvant
Magnesium

• Mechanism
  – N-Methyl-D-aspartate (NMDA) antagonist: moderating calcium influx into neurons
  – decrease peripheral nerve excitability and to enhance the ability of LA to raise the excitation threshold of A-beta fibers

• Literature:
  – consistently prolongs peripheral nerve blocks
  – no adjuvant-related toxicity or side effects
  – little more nausea with 200mg, but not with 150mg
# Magnesium

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Anesthetic</th>
<th>Site/Dose</th>
<th>Prolongation of Analgesia or Sensory Block</th>
<th>Side Effects &amp; Toxicity</th>
<th>Systemic Control (route)</th>
<th>Jadad Scale (I-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elshamaa HA et al</td>
<td>Bupivacaine 0.25% [102]</td>
<td>Femoral-500mg</td>
<td>10h*, 2h***</td>
<td>Not reported</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Lee AR et al</td>
<td>Bupivacaine 0.5% [103]</td>
<td>ISB- 200mg</td>
<td>2h*</td>
<td>Nausea 2-3x more frequently at 4, 8, and 12hrs postoperatively with magnesium</td>
<td>No</td>
<td>V</td>
</tr>
<tr>
<td>Gunduz A et al</td>
<td>Prilocaine 2% [104]</td>
<td>Axillary-150mg, 100mg</td>
<td>2h***, 1h***</td>
<td>None</td>
<td>Yes (150mg IV)</td>
<td>II</td>
</tr>
<tr>
<td>Dogru K et al</td>
<td>Levobupivacaine 0.5% [105]</td>
<td>Axillary- 150mg</td>
<td>150min***</td>
<td>No thrombi or vasospasm in any group. Other side effects not reported.</td>
<td>No</td>
<td>III+</td>
</tr>
<tr>
<td>Dogru K et al</td>
<td>Levobupivacaine 0.25% [105]</td>
<td>Axillary- 150mg</td>
<td>100min***</td>
<td>No thrombi or vasospasm in any group. Other side effects not reported.</td>
<td>No</td>
<td>III+</td>
</tr>
</tbody>
</table>

*Time to first analgesic;  
**Time to first reported pain;  
***Time to pinprick or restoration of sensation.

Kirksey, M.A. et al., 2015. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: A systematic qualitative review. *PLoS ONE.*
Magnesium

• Conclusion:
  – potential neurotoxicity and side effects of peripherally administered magnesium have not been adequately studied
  – clinical efficacy can be achieved with lower doses of magnesium while avoiding the side effects of nausea and vomiting
Ketamine

- **Mechanism:**
  - NMDA receptor antagonist with LA-properties

- **Literature:**
  - Limited data on the effect of ketamine as a perineural additive
  - High incidence (44%) of adverse effects such as hallucinations, drowsiness, and nausea with no prolongation of analgesia

- **Conclusion:**
  - Not recommend its use or further clinical study as a perineural adjuvant
Neostigmine

• Mechanism:
  – acetylcholinesterase inhibitor: increasing endogenous acetylcholine at the nerve terminal

• Literature:
  – failed to increase block duration
  – relatively high incidence of nausea and associated gastrointestinal (GI) distress
  – similar level of neurotoxicity as midazolam
Future?

- Liposomal-bupivacaine = EXPAREL
- SABER-Bupivacaine = POSIMIR/POSIDUR
Liposomal-bupivacaine = EXPAREL

- **DepoFoam technology:**
  - multivesicular liposomes
  - slow release over days

- **Dose?**
  - 1 flacon 20ml = 266mg bupivicaine = max recommended dose
    → volume expansion: up to 280ml NaCl 0,9% may be added
    → volume expansion does not appear to affect its clinical efficacy or pharmacokinetic profile
Liposomal-bupivacaine = EXPAREL

- Pharmacokinetics:

SABER-Bupivacaine = POSIDUR

- Extending duration analgesia to 3 days
  - bupivacaine base 1,3%
  - fully esterified sugar derivate
    - sucrose acetate isobutyrate (SAIB) + benzyl alcohol

Conclusions

• Recommended:

<table>
<thead>
<tr>
<th>Adjuvants</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Modest efficacy at best (onset time + prolongation)</td>
</tr>
<tr>
<td></td>
<td>Low dose 100µg to avoid side-effects</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Off-label use perineural</td>
</tr>
<tr>
<td></td>
<td>Recommended intravenous use with good results</td>
</tr>
<tr>
<td></td>
<td>4mg as good as 8mg</td>
</tr>
</tbody>
</table>

• Maybe:

<table>
<thead>
<tr>
<th>Adjuvants</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>Off-label use with promising results</td>
</tr>
<tr>
<td></td>
<td>More data needed for safe perineural use</td>
</tr>
<tr>
<td></td>
<td>May increase bradycardia and sedation intraoperatively</td>
</tr>
<tr>
<td>Buprenorpine</td>
<td>Promising but small number of patients</td>
</tr>
<tr>
<td></td>
<td>Larger studies needed</td>
</tr>
<tr>
<td></td>
<td>PONV prevention</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Dose 150mg good results, but to little data about neurotoxicity</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Ultrasound guided: possible detrimental on nerve and minimal effect</td>
</tr>
<tr>
<td></td>
<td>Neurostimulator: use as intravascular marker</td>
</tr>
</tbody>
</table>
Conclusions

- Avoid:

<table>
<thead>
<tr>
<th>Adjuvants</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Inconsistent results with side effects of opioids</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1-2min shortening onset time</td>
</tr>
<tr>
<td></td>
<td>no effect on block duration</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Possibly neurotoxic, should be avoided</td>
</tr>
<tr>
<td>Ketamine</td>
<td>High incidence of adverse events, no prolongation of analgesia</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Failed to increase block duration</td>
</tr>
<tr>
<td></td>
<td>high incidence of nausea and GI distress</td>
</tr>
</tbody>
</table>
Bibliography


