No-Nonsense Recommendations on Local Anesthetic Additives: What Really Works and What Does Not

Faraj Abdallah, MD  University of Toronto

Outline

- Defining the need
- Feasible options
  - Dexamethasone
    - Evidence strength
    - Evidence weaknesses
    - Persistent concerns
    - Clinical recommendations
  - Dexmedetomidine
    - Evidence strength
    - Evidence weaknesses
    - Persistent concerns
    - Clinical recommendations
- Future research directions

Disclaimer

- The views and opinions presented here represent those of the speaker and should not be considered advice or guidance on behalf of the organizers of this event.
- No conflicts of interest.

Where applicable:

- DexA: Dexamethasone
- DexM: Dexmedetomidine
- GA: General Anesthesia
- RA: Regional Anesthesia
- s-PNB: Peripheral Nerve Block
- PPP: Persistent post-surgical pain
- RCT: Randomized Controlled Trial

Why are adjuncts needed?
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- Proportion of ambulatory procedures grew from 38.6% to 57% bet. 1996-2006.
- Projected to grow from 57% to 64% between 2006-2016.


Role of acute post-surgical analgesia in success of ambulatory surgery

- Failure in ambulatory surgery = i) prolonged hospital stay or ii) unplanned admission or iii) readmission

- Causes (most common to least common)
  - Post-operative pain
  - Post-operative nausea and vomiting
  - Dizziness
  - Drowsiness
  - Cognitive dysfunction
  - Cardiovascular events
  - Type of surgery
  - Anesthetic technique


Why are adjuncts needed?

Persistent post-surgical pain (PPP)

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Incidence of chronic pain (pain lasting &gt; 3 months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>85%</td>
<td>Acta Pain 2006; 6: 45—53</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>65%</td>
<td>Br J Anaesth 2008; 101: 77-86</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>55%</td>
<td>Clin J Pain 2003;19.1: 48-54</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>50%</td>
<td>Br J Anaesth 2008; 101: 9-15</td>
</tr>
<tr>
<td>Major abdominal surgery</td>
<td>45%</td>
<td>Pain 2001; 82:23–4</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>40%</td>
<td>IASP Press; 2001. p. 151—64</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>20%</td>
<td>IASP Press; 2005. p. 460</td>
</tr>
<tr>
<td>Brain injury surgery</td>
<td>20%</td>
<td>JAMA 2009; 302: 1985-92</td>
</tr>
<tr>
<td>Cataract</td>
<td>15%</td>
<td>IASP Press; 2005. p. 151-4</td>
</tr>
</tbody>
</table>

Reference


Role of acute post-surgical analgesia in preventing PPP

- Transition from Pre-emptive Preventive (prolonged effective) analgesia.

- Prolonged and effective acute pain relief reduces the risk of sensitization and developing chronic post-surgical pain.


Is it RA effective?
Is RA effective?

- Multimodal analgesia inclusive of RA is the most effective pain relief strategy.

Is it prolonged?

- Short answer: No (most of the time)
- Duration of moderate-severe pain >> duration of RA

Is the duration of pain relief produced by RA sufficient?

- Analgesic benefits of RA are:
  - short-lived
  - limited by the duration of action of currently available local anaesthetics
  - block resolution prior to the period of worst postoperative pain

Conclusion

There is a clear need for prolonging the duration of effective analgesia for outpatient procedures performed in the setting of RA.

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    - Potential concerns
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  - Dexmedetomidine
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    - Potential concerns
    - Clinical recommendations
- Future research directions
Prolonging the duration of analgesia

- Options:
  1. Continuous catheter-based blocks
  2. Liposomal bupivacaine
  3. Adjuvants

Toward Outpatient Arthroplasty: Accelerating Discharge With Ambulatory Continuous Peripheral Nerve Blocks

- Robert P. McGraw, III, MD
- Brian M. Ilfeld, MD, MS

American Society of Regional Anesthesia and Pain Medicine 2010 Gaston Labat Lecture
Perineural Catheter Analgesia as a Routine Method After Ambulatory Surgery—Effective But Unrealistic

- Narinder Rawal, M.D., Ph.D.

Are catheters the answer?

- Continuous blocks can extend postoperative analgesia
- But placement requires additional time, cost, and skill
- And use in outpatient setting is subject to a tight selection criteria

Is liposomal bupivacaine the answer?

- Tight selection criteria for ambulatory catheters requires patients to:
  - Comprehend and adhere to the analgesic plan
  - Ambulate independently
  - Care for the pump and catheter site on their own
  - Be within contact with healthcare providers
  - Return for additional medical care, if necessary

- Unlikely!
  - Expensive
  - Not available in all centres
  - FDA-approved for infiltration
  - Perineural use requires investigational drug licence (IND)
  - Undesirable prolongation of motor blockade duration.
What about adjuvants?

- Several local anesthetic adjuvants have been investigated in an attempt to prolong the duration of nerve blocks:
  - Buprenorphine
  - Clonidine
  - Dexamethasone
  - Dexmedetomidine
  - Magnesium
  - Midazolam

- Outcome: Varying degrees of success

Profiles of adjuncts

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Evidence of efficacy</th>
<th>Adverse events</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Clonidine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Dexamethasone</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Magnesium</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Midazolam</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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- Future research directions

What is attractive about DexA?
- Safe
- Simple
- Available
- Cheap
- Routinely used (anti-emetic)
- Has an intrinsic analgesic effect

Evidence strength

- Concurrent results from 6 systematic reviews
  - 4mg perineural dose is effective
  - Successful with both intermediate- and long-acting local anesthetics
  - Prolongs the duration of analgesia by at least 50% (up to 200%)
  - Prolongs both sensory and motor blockade duration (undesirable)
  - No added benefit with higher doses
  - No adverse reactions
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Evidence weakness
- Off-label use:
  - So are epidural steroids!
  - Major journals no longer require an IND
- Heterogeneous (I^2 >90%)
  - Level 1a- evidence
  - Level D recommendations (weak)
  - Intrinsic limitation of evidence (small trials)
- Majority of evidence relates to brachial plexus (limited truncal and lower extremity RCTs)

Concerns
- Safety:
  - Safe at clinical doses used
  - Safe at higher doses
    - Chronic pain literature
      - Interlaminar epidural
      - Transforaminal epidural
      - Nerve root injection
    - Routinely use 30-80 mg doses of methylprednisolone, benzylprednisolone, or triamcinolone
    - Repeated twice, with 3-week intervals.
      - Pain Physician 2007; 10:185-212

Concerns
- Safety: Preservatives
  - Much lower concentrations are used now (0.1% vs. 1.5% in case report).
  - A total of 8/23 RCTs reviewed did not use preservative-free DexA
    - Including our own work

Concerns
- Avoid in diabetic patients
- May reduce blood flow to neural tissue
  - Avoid in diabetics
  - Do not mix with epinephrine

Concerns
- May be associated with rebound pain when a 4mg dose is used, 2mg dose is preferred.
  - Based on QI surveys
  - Clinically not important difference in pain
  - May be explained by non-compliance with analgesics
  - Controverted by 23 RCTs
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Alternatives to perineural administration

- Emerging evidence indicates that systemic DexA can be an effective alternative to the perineural route.
  - Supported by 3 RCTs
  - Lack of difference between two routes can be due to underpowered trials (small difference)
    - A small difference is OK if avoiding the perineural route is a priority.

Recommendations

- A 4mg dose of perineural DexA is a safe and effective way of prolonging the duration of s-PNB.
- Efficacy of the systemic route of administration requires further exploration.

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What is attractive about DexM?

- Safe
- Simple
- Available
- Routinely used (sedation)
- Anti-inflammatory effect
- Has an intrinsic analgesic effect

Evidence strength

- Total of 21 RCTs:
  - Brachial plexus blocks
  - Local anesthetic vs. local anesthetic + DexM

Concurrent evidence from 21 RCTs:

- 0.5 µg / kg DexM (single bolus) applied perineurally is effective
- Successful with both intermediate- and long-acting local anesthetics
- Prolongs the duration of analgesia and sensory block by at least 50% (up to 100%)
- Adverse effects: sedation, hypotension, and bradycardia
- Possible dose-response
- Differential prolongation (sensory > motor) ?

Evidence strength
## Evidence Weakness

- **Off-label use:**
  - Requires FDA IND licence (IV sedation = only approved use)

- **Heterogeneous (I² > 90%)**
  - Level 1a evidence
  - Level D recommendations (weak)
  - Intrinsic limitation of evidence (small trials)

- Majority of evidence relates to brachial plexus (limited truncal and lower extremity RCTs)

## Evidence Weakness

- Only 2 of 21 trials had an IND-equivalent obtained from the national health authorities

- Mostly in low-impact journals

- Inconsistent doses (0.1 µg/kg up to 3 µg/kg)

- Inconsistent assessment of sensory block duration

## Desirable Characteristics

- Attenuates local anesthetic induced inflammatory response in peripheral nerves
  - Potential implications on rebound pain and PPP

## Concerns

- Limited safety data for prolonged infusion

- Bradycardia and hypotension
  - Avoid if significant baseline bradycardia/hypotension, bradyarrhythmias
  - Caution with profoundly β-blocked patients
  - Additional vigilance when used for shoulder surgery in the beach-chair position

## Alternatives to perineural administration

- Previously suggested by Marhofer et al.

## Clinical Implications

- DexM may offer a better adjunct profile than DexA:
  - Anti-inflammatory effect
  - Hypnotic (sedation for surgical blocks)
  - Differential block prolongation (sensory >> motor)
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Recommendations

Despite the acknowledged limitations of available evidence:

• A 0.5 µg / kg perineural dose of DexM is a safe and effective way of prolonging the duration of s-PNB.

• Efficacy of the systemic route of administration requires further exploration.

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Future research directions

• Dose-ranging research to:
  ○ Confirm dose-effect for DexM
  ○ Determine minimal effective dose of DexA (2 mg?)
  ○ Determine the doses that constitute an ideal compromise between prolonging the duration of analgesia without prolonging motor blockade.

• Systemic vs. perineural comparisons to confirm the efficacy of the systemic route

• Investigate synergistic effect between different adjuncts

Future research directions

• Synergism:
  • Midazolam-Clonidine-Buprenorphine-Dexamethasone adjunct combination:
    ○ Safe
    ○ May be effective enough to allow using very low concentrations of local anesthetic (e.g. 0.1%), advantageous in ambulatory settings.


Additives in Regional Anesthesia and Analgesia: Important Considerations

Jacques T. Salama, MD, Anesthesiological Research Program, University of Toronto, Toronto, Ontario, Canada; and Department of Anesthesiology, University of Toronto, Toronto, Ontario, Canada;

Inconclusive, suggestive of synergism between Dexamethasone and buprenorphine


Future research directions

Synergism:

Inconclusive, suggestive of synergism between Dexamethasone and buprenorphine

Thank you!