Spinal Anaesthesia
Newer Developments – Role of Adjuvants

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ESRA Past President
Adjuvant Drugs for RA

- **Prolong** local anaesthetics’ analgesia and avoid their toxic doses
- **Reduce** the incidence of inadequate analgesia

Improvement of success of regional anaesthesia

Vadalouca A, 2002
Nerve Blockade

- Complete
- Reproducible
- With the desired duration of action
In the past

New local anaesthetics with

- Better spread
- Good separation of sensory and motor block
At present

2\textsuperscript{nd} drug added to local anaesthetic

\textbf{adjuvant drug}

- ↓ sensory input to CNS
- Improve the success of regional anaesthesia
- Action at secondary site different to LA
Adjuvant Drugs for Regional Anaesthesia that are in use

- Vasoconstrictors
- Opioids
- a2 – adrenergic agonists
- NMDA receptor antagonists
- Anticholinesterase drugs, cholinergic agonists

Vadalouca A, 2002
In the Future

Adjuvant Drugs

- Calcitonin
- Octreotide
- Adenosine
- Antioxidants
- Ziconotide
Ziconotide

- N – Type calcium channel blocker
- Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or aids: randomized, controlled trial

Staats P et al, JAMA 2002
Vasoconstrictors

- For many years the only adjuvant drugs used in RA
- Even today they are commonly used
Vasoconstrictors

- Prolongation of blockade period by approximately 50%
- Decrease of the systemic absorption of LA by approximately one third

Scott DB et al, 1972
Mean Maximum Values
Lignocaine 20 ml (400 mgr)

Scott DB et al, 1972
Doses of epinephrine in LA solutions

- LA solutions + Epinephrine 1:200,000 (5mcg/ml) → Classic mixture
- Lignocaine +
  - Epinephrine 1:200,000
  - Epinephrine 1:400,000
  - Epinephrine 1:600,000

DiFazio CA et al, 1986
Doses of epinephrine in LA solutions in OBSTETRICS

- LA solutions + Epinephrine 1:200,000 (5mcg/ml) → Classic mixture

- Lignocaine + Epinephrine 1:600,000
  Preferred especially in preeclamptic patients

Alahuhta S et al, 1991
Doses of epinephrine in LA solutions in OBSTETRICS

Labour Pain

- Bupivacaine 12.5 mgr (0.125%)
- Epinephrine 12.5 mcg (1:800,000)

A. Van Zundert, 1996
Epinephrine in LA solutions in the subarachnoid space

- Greater duration of sensory anaesthesia in the lower extremities
- Increased rate of success of spinal anaesthesia
- Significant prolongation with 0.6 mcg epinephrine added to 60 mgr hyperbaric lignocaine for spinal anaesthesia in thoracic dermatomes

Carpenter RL, 1989
Kito K et al, 1998
Epinephrine in LA solutions in the subarachnoid space

Epinephrine + Procaine for spinal anaesthesia

- Prolongs sensory & motor blocks by 25%
- ↑ incidence of nausea
- ↓ possibility of systemic toxicity

Bergeron L et al, 1999
Combined use of epinephrine with hyperbaric tetracaine in the supine position can enhance the cephalad spread of sensory block levels compared with hyperbaric tetracaine alone in the lithotomy position.

Inoue S et al, 2004
Acta Anaesth Scand
Hyperbaric spinal 2 – chloroprocaine:

- Effective
- Anaesthetic profile appropriate for case in the surgical outpatient
- Over the dose range 30 – 60 mgr

Addition of epinephrine

- Not recommended
- Frequent incidence of side effects

Smith KN et al, 2004

Anaesth Analg
Intrathecal Epinephrine

- **Augments the sedative effect** of propofol during spinal anaesthesia
- **Augments the depression of BIS** during intraoperative propofol sedation

Yotsui T et al, 2004
Opioids as Adjuvant Drugs in RA

- Opioids in epidural – subarachnoid anaesthesia
- Opioid receptors in substantia gelatinosa of the spinal cord
  Rexed Lamina II - III

Cousins MJ, 1984
Action of opioids

- Brain Stem
- Spinal Cord
- Peripheral Sites

Stein C, 1993
Opioid Receptors

- \( \mu \) – receptors (\( \mu_1 \) & \( \mu_2 \))
- \( \delta \) – receptors
- \( \kappa \) – receptors

Atcheson R et al, 1994
Bupivacaine

+ 

Fentanyl
10 – 30 mcg/h

Sufentanil
1 – 3 mcg/h

↓ 30% the dose of LA

Atcheson R et al, 1994
Side Effect Profiles are similar although sufentanil > fentanyl for respiratory depression

Norris M et al, 1994
Hermann N et al, 1999
Spinal Anaesthesia

Bupivacaine 0.5% (12.5 mgr) + Morphine 0.2 mgr → Good Analgesia
→ Fewer Side Effects

Rodanant O et al, 2003
Spinal in the elderly

4 mgr Bupivacaine + 25 mcg fentanyl

- Adequate Analgesia
- Fewer Side Effects
- Prostatectomy

Kararmaz A et al, 2003
The addition of fentanyl (25 mcg) to hyperbaric bupivacaine (10 mgr) & limiting the spread of the block does not improve either haemodynamic or pulmonary function compared with bupivacaine 15 mgr in transurethral prostatectomy.

Walsh KH et al, 2003
Outpatient Surgery

- Attention to technique
- Reduction of dose
- Addition of fentanyl to lignocaine
- Effective spinal anaesthesia
- Rapid recovery
- Few side effects - complications

Urmey WF et al, 2003
Labour Analgesia

- **Spinal:** Bupivacaine 2 mgr + 12.5 mcg Fentanyl
  
  Labour Analgesia for 85 min

- **Epidural:** Morphine 125 mcg
  
  improves pain control

*Hess PT et al, 2003*
Sufentanil 5 & 7.5 mcg

+ Hyperbaric Bupivacaine 0.5% (12.5 mgr)

- Adequate analgesia for CS
- Good post-operative analgesia
- 7.5 mcg → pruritus

Brage AF et al, 2003
- Bupivacaine 0.25 mgr
- Adrenaline 25 mcg
- Sufentanil 2.5 mcg
- Bupivacaine 1.25 mgr
- Adrenaline 12.5 mcg
- Sufentanil 10 mcg

Spinally

VAS < 2 → ± 140 min

Epidural Top-up

VAS < 2 → ± 120 min

Albert Van Steenberge, 1998
Spinal anaesthesia for appendicectomy

Hyperbaric bupivacaine 0.5% (4 ml) + fentanyl (20 mcg)

- Improved quality of anaesthesia
- Prolonged duration of analgesia
- Delayed analgesic requirement in the early postoperative period
- Less shivering in the fentanyl group

Techanirate A et al, 2004
Spinal 2 – chloroprocaine (40 mgr)

- Rapid onset
- Reliable anaesthesia
- No signs of transient neurological symptoms

Addition of fentanyl
- Lengthening of the regression to L1 dermatome
- Lengthening of tourniquet time
- Minimally increased duration of block

Vath JS et al, 2004
$a_2$ – adrenergic agonists as adjuvants in RA

- Mostly $a_2$ – adrenergic agonists: clonidine, dexmetomididine, tizanidine
- Reduction of sympathetic nervous system output from CNS
- Also antihypertensive drugs
- 1984: first time clonidine was used epidurally (Torsten Gordth)
- Analgesia, no adverse effects of opioids
- But: hypotension & dry mouth

Eisenach JC et al, 1996
Clonidine in the epidural / subarachnoid space

- **Dose-dependent Analgesia**
- **Does not produce**
  1. Ventilatory Depression
  2. Pruritus
  3. Nausea
  4. Vomiting

Filos K et al, 1994
Eisenach J, 1996
Asai et al, 1997
Clonidine as an adjuvant in RA in children

The use of clonidine as an adjuvant drug in the field of regional anaesthesia in children seems to be very effective and safer than opioids and adrenaline.

Ivani G et al, 1998
Clonidine 1 mcg/kg, added to spinal isobaric bupivacaine doubles the duration of the block in the neonates without significant deleterious haemodynamic or respiratory effects.
Clonidine administration through various routes

There is clear evidence that a fixed dose of clonidine im, epidurally or intrathecally has a clear order of duration:

- **Intrathecal > epidural > im**
- Thus supporting intrathecal administration

Bernard JM et al, 1995
Eisenach JC, 1998
Clonidine

Spinal (Inguinal Hernioraphy)

Hyperbaric Bupivacaine (6 mgr) + clonidine 15 mcg

- ↑ Spread of analgesia
- Prolongs time to 1st analgesic request
- ↓ post-op pain

Dobrydnjov I et al, 2003
Clonidine

Intravenous: 3 mcg/kg

1h after spinal block

- Prolongs bupivacaine spinal anaesthesia for 1h approximately
- Without adverse effects

Rhee K et al, Acta Anaesth Scand 2003
Clonidine

Spinal (Total Knee Arthroplasty)

Hyperbaric Bupivacaine (15 mgr) + clonidine 25 or 75 mcg + morphine 250 mcg

Post-operative analgesia improvement compared with intrathecal morphine alone

Sites BD et al, 2003
Clonidine
Lower Spine Procedures

Epidural administration: 150 mcg
Supplement to spinal anaesthesia

- No perioperative complications
- Improved Postoperative Pain
- Haemodynamic Stability

Jellish WS et al, 2003
Clonidine + Opioids
(Continuous Epidural Infusion)

↓ 20 – 30 % of opioid dose

Eisenach JC, 1998
LA + Clonidine

Labour Analgesia

**INCREASED:**
- Risk of maternal hypotension
- Risk of maternal sedation
- Risk of neonatal sedation

Eisenach JC, 2000
Clonidine in obstetrics
(Labour)

**PCEA**
- bupivacaine
  - + clonidine
  - + fentanyl

Supplementation rate of analgesics
Reduce
Shivering

Paech JM et al, 2000
CSE in Obstetrics

- 9 – 10 mgr ropivacaine
  + 25 mcg fentanyl

- 100 mcg fentanyl
  + 30 mcg clonidine

Spinally

Epidurally

Vadalouca A et al, 2000
Other uses of clonidine as an adjuvant

- **Local infiltration** with LA + clonidine: better results in comparison with plain LA
- **During iv anaesthesia** clonidine improves the tolerance of tourniquet

Elliot S et al, 1997
Gentilli M et al, 1998
# Dexmetomidine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clonidine</th>
<th>Dexmetomidine</th>
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<tbody>
<tr>
<td>Type of action</td>
<td>$a_2$ selective adrenergic agonist</td>
<td>$a_2$ selective adrenergic agonist</td>
</tr>
<tr>
<td>Cardiovascular blood pressure</td>
<td>moderate</td>
<td>minimal in comparison with clonidine</td>
</tr>
<tr>
<td>effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>few</td>
<td>fewer</td>
</tr>
<tr>
<td>Selectivity for $a_2$ receptors</td>
<td>$a_2$ - agonist</td>
<td>7 times more selective</td>
</tr>
<tr>
<td>Duration of action</td>
<td>short</td>
<td>shorter</td>
</tr>
<tr>
<td>Use in obstetrics</td>
<td>few references</td>
<td>not yet</td>
</tr>
</tbody>
</table>
Ketamine as an adjuvant in RA

- Classic iv drug
- Anaesthetic
- Sedative
- Amnesic
- Analgesic
- Phenylcycloclidine derivative
- Produces dissociative anaesthesia
- S+ & R- isomers
- NMDA receptor antagonist
- 1984 first use intrathecally (Bion)
Use of ketamine Intrathecally

- **Surgical anaesthesia** can be achieved by **intrathecal ketamine**
- Intraspinal ketamine in pigs produced **lower haemodynamic alterations** in comparison with lignocaine.
- **Haemodynamic alterations, not dose-dependent**
- **?? Neuraxial Ketamine in hypovolaemic patients**

Errando CI et al, 2000, 2004
Intrathecal ketamine: a promising analgesic alternative for women in labour, although its use is still at an early clinical stage

Mercier FJ et al, 1998
**Ketamine as an adjuvant in children**

- **Epidural route**
  - **0.5 mg/kg**
- **Caudal route**
  - Postoperative analgesia

- **Sedation / Analgesia**
  - **1 – 2 mg/kg iv**

- **ICU**
  - (continuous infusion)
  - **0.5 mg/kg/h**

*Ivani G et al, 2003*
Ketamine (spinally – epidurally)

- **Intrathecal** Ketamine + Bupivacaine (spinal anaesthesia)
- **Epidural** Ketamine + LA

Better post-op analgesia
Alternative to opioids for obstetric anaesthesia

Kethirrel S, 2000
Himmelscher, 2001
$S\ (+)\text{Ketamine}$ (spinally – 0.1 mgr/kgr) + hyperbaric bupivacaine 7.5 mgr

- **Patients > 60 years**
  - Provide

  - shorter motor / sensory block
  - shorter duration of action
  - less motor blockade in elderly males

  Togal et al, 2004
Analgesic Affinity of Ketamine

- Antioxidative Properties

Lupp A et al, 1998
NMDA antagonists as antioxidants

- Antioxidants play a role in pain relief
- New horizon for analgesic properties of NMDA antagonists

Kahlil Z et al, 1999
Neostigmine as an adjuvant in RA

- Neostigmine administered spinally

  *inhibits nociception* in a dose-dependent manner by increasing the endogenous neurotransmitter acetylcholine

Hood DD et al, 1996
Neostigmine as an adjuvant in RA

- However: scepticism about side effects
- Need to investigate the ultra low doses of neostigmine combined with other analgesics in order to avoid adverse effects

Eisenach JC, 2000
Low – Dose Spinal Neostigmine: Morphine Analgesia Improvement

- 1 – 5 mcg neostigmine
  + 100 mcg morphine

- Doubled the duration to first rescue analgesic
- ↓ analgesic consumption in 24 h
- No increase in adverse effects

Almeid RA et al, 2003
**Neostigmine** as an adjuvant in obstetrics (labour)

- bupivacaine + fentanyl
  + neostigmine + clonidine

- ↑ duration of labour analgesia
- ↑ nausea

Owen MD et al, 2000

Intrathecally
Adenosine receptors and pain signaling

- **Adenosine receptors**: in the superficial layers of the dorsal horn of the spinal cord
- Antinociceptive effect of adenosine: probably mediated through $A_1$ subtype receptors
- *It increases the pain threshold*

*Sjolund KF et al, 1998*
Adenosine intrathecally

- 2000 mcg intrathecally: transient lumbar pain
- Adenosine: no motor block, no hypotension, no sedation
- Analgesia in hypersensitivity states
- Uncertain role in acute obstetric pain

Karlsten R et al, 1995
Rane K et al, 1998
Chiari A et al, 1999
Reports: Alleviation of post-operative and severe cancer pain if given epidurally - intraspinally

Chrubasic, 1989
Vadalouca A, 1993
Epidural – Spinal Calcitonin

- Rich literature regarding spinal and epidural administration for cancer pain
- Few references regarding its successful use in post-op pain

Fiore CE et al, 1983
Vadalouca A et al, 1999
Vadalouca A et al, 2003
Antioxidants

- They may indicate a new horizon for analgesia
- Can be easily used in some kinds of chronic pain

Davis RH et al, 1990
Alindon TE et al, 1992
Kahlil Z et al, 1999
Perioperative & post-operative pain is a definite fact
Regional anaesthesia:
mostly achieved with LA

Adjuvant drugs:
★ Better analgesia
★ Prolonged analgesia
“All daring actions begin from necessities”

Evripides

When safer & better RA is the primary goal

non-traditional adjuvants
Future studies are increasingly important to monitor the **risk-to-benefit ratio** from the use of **Novel Adjuvant Drugs**.