ASMIC 2016

DEXMEDETO MIDINE
IN THE INTENSIVE CARE UNIT

DR KHOO TIEN MENG
PREAMBLE : EVOLUTION OF SEDATION IN THE ICU

• 1980s : ICU sedation largely extension of GA
  - No standard approach, highly variable
  - Deep sedation levels, neuromuscular blockade

• Last 2 decades : paradigm shift in practice
  - Sedation scoring systems
  - Delirium recognition and treatment
  - “Sedation minimisation strategies”
    ✓ Intermittent sedation
    ✓ Daily interruption of sedation
    ✓ Goal directed sedation
    ✓ Analgesia 1st sedation
PREAMBLE : EVOLUTION OF SEDATION IN THE ICU

• Pain, Agitation & Delirium Guideline (2013) :
  “We recommend that sedative medications be titrated to maintain a light rather than deep level of sedation”

• Except for specific situations (eg severe ARDS, head trauma), goal of sedation is a calm, but rousable pt, who should be able to communicate
PREAMBLE : EVOLUTION OF SEDATION IN THE ICU

- Benzodiazepines & propofol became standard of care ..........**HOWEVER** ........
- Benzodiazepines $\rightarrow$ unpredictable accumulation, prolonged sedation, **DELIRIUM**
- Propofol $\rightarrow$ hypotension, hypertriglyceridaemia, **PRIS**
- Newer sedative agents will be compared against the standard for efficacy & safety
- Dexmedetomidine : necessitated comparisons with standard care ie benzodiazepines & propofol
DEXMEDETOMIDINE is an $\alpha_2$ adrenoceptor agonist
MAIN SITE OF ACTION IS THE LOCUS COERULEUS

• Pontine nucleus
• Largest group of noradrenergic neurons
• High density of $\alpha_2$ adrenoceptors
• Extensive projections to brain & spinal cord
• 2 main functions :
  ➢ Arousal / vigilance
  ➢ Autonomic regulation
PHARMACOLOGY OF DEXMEDEDETOMIDINE

• Highly selective centrally acting $\alpha_2$ receptor agonist
• Unique mechanism of action primarily on locus coeruleus (other sedatives target GABA receptor)
• $\alpha_2$ adrenoceptor activation $\rightarrow$ reduce LC activity and sympatholytic effects
• Sedative, hypnotic, analgesic, sympatholysis
• $\alpha_2$ receptors on vascular smooth muscle cells $\rightarrow$ vasoconstriction
PHARMACOLOGY OF DEXMEDETOLOMIDINE

• “Rousable/cooperative sedation”
  – Achieve sedation, yet still easily arousable
  – No respiratory depression

• EEG studies:
  – Sedation mimics natural sleep
  – Preservation of slow wave (non-REM) sleep

• Lab/animal studies
  - anti-inflammatory, preserve neutrophil function
  - possible neuroprotection
CARDIOVASCULAR EFFECTS: BP and HR

Heart Rate

Mean Arterial Pressure

plasma dexmedetomidine (ng/ml)

n=10

Baseline 0.7 1.2 1.9 3.2 5.1 8.4 14.7

time (min) post infusion

20 50 90 120 150 180 210

mm Hg

b/min
Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects

NO LOADING DOSE GIVEN

Fig. 2 Haemodynamic parameters during the first 24 h after the start (arrow) of dexmedetomidine. The parameters are shown every 15 min during the first 2 h, then hourly. Values are expressed as mean±1 standard deviation.

Fig. 3 Haemodynamic parameters reported from 24 h until 120 h. Values are expressed as mean±1 standard deviation.
- Prolonged infusions up to 7 days
- **NO LOADING DOSE**
- Dose range 0.2 – 0.7 ug/kg/hr
- *Predictable decreases in BP & HR, but onset was slower and less pronounced*
- *No evidence of rebound hypertension & tachycardia*
Can dex reduce delirium?
Possible ways

- Lacks anticholinergic effects
- Lower opioid requirements
- Promote more physiologic sleep
- ? Neuroprotective
- Avoid sedative agents with greater delirium potential (eg GABA agonists)

Better outcomes? What do the trials say?
Maximizing Efficacy of Targeted Sedation & Reducing Neurological Dysfunction (JAMA 2007)

Hypothesis: Dex, when compared with BZD, reduces delirium & coma while effectively sedating ventilated pts

Medical & surgical ICU pts in 2 tertiary centers

Adult ICU pts requiring ventilation > 24hrs randomised to receive either lorazepam (51 pts) or dexmedetomidine (52 pts)
Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients
The MENDS Randomized Controlled Trial

- Maximum time allowed for study drug infusion – 5 days
- Primary outcome: delirium-free & coma-free days
  (delirium = CAM-ICU +ve; coma = RASS -4 to -5)
- Primary outcome: efficacy of sedation drug in achieving target sedation goals (ability to achieve sedation score within 1 point of desired goal)
Dex: more frequently within 1 point of RASS goal

Dex: > twice as many delirium- & coma-free days
Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients
The MENDS Randomized Controlled Trial

• Conclusions:
  – Lorazepam: more oversedation / coma
  – Dexmedetomidine: more days without delirium or coma and higher accuracy at meeting sedation goals
Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients
A Randomized Trial

- SEDCOM : Safety & Efficacy of Dexmedetomidine Compared with Midazolam (JAMA 2009)
- Hypothesis : sedation strategy using dexmedetomidine will result in improved outcomes compared with midazolam
- Prospective RCT, 68 centers, 5 countries
- Medical & surgical ICU, anticipated ventilation > 3 days
- Randomisation 2:1 fashion to obtain more comprehensive safety data on prolonged dexmedetomidine use
- Study drug infusion up to 30 days
- Dose up to 1.4μg/kg/hr
Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients
A Randomized Trial

- Dexmedetomidine 244 pts, midazolam 122 pts
- Primary endpoint: sedation efficacy i.e. percentage of time within target sedation range (RASS score -2 to +1)
- Secondary endpoints: prevalence & duration of delirium
- Others: duration of ventilation, ICU length of stay, CV safety data, sepsis
• %time within target RASS: no difference between 2 groups
• Median time to extubation 1.9 days shorter for dex
• Median ICU LOS similar
• Delirium prevalence: 24.9% reduction
• Daily incidence of delirium after study drug initiation:
  ✓ decreased in dex group
  ✓ Increased in mida group

• Conclusions – dexmedetomidine resulted in:
  – Reduced development of delirium AND improved the resolution of delirium if it develops
  – Shortened time on mechanical ventilation
  – Earlier extubation
Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation
Two Randomized Controlled Trials

- 2 large, parallel, multicenter RCT (Europe & Russia)
- Hypothesis: dexmedetomidine is noninferior to midazolam or propofol in maintaining mild to moderate sedation
- Also assessed benefits in terms of reduced ventilation, length of stay, and pts’ ability to communicate
- ICU pts on invasive ventilation, in clinical need for light to moderate sedation (RASS -3 to 0)
  - **MIDEX**: randomized to midazolam (251 pts) or dexmedetomidine (249 pts)
  - **PRODEX**: randomized to propofol (247 pts) or dexmedetomidine (251 pts)
- Maximum duration of study drug infusion – 14 days
Primary End Points

<table>
<thead>
<tr>
<th></th>
<th>MIDEX</th>
<th>PRODEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of mechanical ventilation (including NIV)</td>
<td>123</td>
<td>164*</td>
</tr>
<tr>
<td>Medetomidine (hrs)</td>
<td>164*</td>
<td>97</td>
</tr>
<tr>
<td>Dex (hrs)</td>
<td>164*</td>
<td>97</td>
</tr>
<tr>
<td>Midazolam (hrs)</td>
<td>164*</td>
<td>97</td>
</tr>
<tr>
<td>Median time to extubation</td>
<td>101</td>
<td>147*</td>
</tr>
<tr>
<td>Medetomidine (hrs)</td>
<td>147*</td>
<td>69</td>
</tr>
<tr>
<td>Dex (hrs)</td>
<td>147*</td>
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</tr>
<tr>
<td>Medetomidine (hrs)</td>
<td>147*</td>
<td>69</td>
</tr>
<tr>
<td>Proportion of time in target sedation range</td>
<td>60.7%</td>
<td>56.6%</td>
</tr>
<tr>
<td>Medetomidine (hrs)</td>
<td>64.6%</td>
<td>64.7%</td>
</tr>
<tr>
<td>Dex (hrs)</td>
<td>64.6%</td>
<td>64.7%</td>
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</tbody>
</table>

* Statistically significant p<0.05
## Ability to Communicate & Cooperate

### Mean (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexmed</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexmedetomidine vs. midazolam</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can the patient communicate pain?</td>
<td>46 (42-53)</td>
<td>24 (20-29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>How arousable is the patient?</td>
<td>58 (54-63)</td>
<td>41 (36-45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>How cooperative is the patient?</td>
<td>45 (40-49)</td>
<td>25 (21-30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Dexmedetomidine vs. propofol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can the patient communicate pain?</td>
<td>49 (45-54)</td>
<td>35 (31-40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>How arousable is the patient?</td>
<td>59 (55-63)</td>
<td>48 (43-52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>How cooperative is the patient?</td>
<td>47 (42-52)</td>
<td>38 (33-43)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Secondary end point**

- assessment of arousal, ability to communicate & cooperate: dex pts more arousable, cooperative, better able to communicate pain
• Conclusions :
  – Dexmedetomidine not inferior to midazolam or propofol for long term (mild-moderate) sedation in ventilated ICU pts
  – Shorten ventilation compared to mida but not propofol
  – Reduce time to extubation compared to both mida & propofol
  – Enhanced ability to cooperate & communicate with staff
Dexmedetomidine for Treatment of Agitation and Bridge to Extubation

Feasibility of dexmedetomidine in facilitating extubation in the intensive care unit

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The effect of dexmedetomidine on agitation during weaning of mechanical ventilation in critically ill patients

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• Evaluated impact of adjunctive dexmedetomidine in pts who were difficult to wean from mechanical ventilation due to agitation
• Authors concluded that dex is viable adjunctive option to aid in extubation for pts experiencing agitation
Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium
A Randomized Clinical Trial

- **DahLIA :** Dexmedetomidine to Lesson ICU Agitation
- **Hypothesis :** In pts who remain intubated because of severe agitated delirium, dexmedetomidine, when added to standard care, would result in shorter duration of delirium and earlier extubation
- **Double blind, placebo-controlled, multicenter RCT**
- **Adult ICU pts who were candidates for extubation based on CV, resp and metabolic criteria, BUT had to continue ventilation because of severe degree of agitation**
- **Randomised to dexmedetomidine (39 pts) or saline placebo (32 pts)**
Delirium resolved more rapidly (23.3 vs 40.0 hrs), difference 16 hrs, p=0.01

Delirium for a lower proportion of their ICU stay (median of 2 additional delirium-free days)

**CONCLUSION:**

In patients with agitated delirium receiving ventilation - compared with placebo, dexmedetomidine hastened resolution of delirium & extubation

Earlier extubation (21.9 hrs vs 44.3 hrs); difference 19.5 hrs, p<0.001
Summary/Key Additional Points to Take Home

• Cannot achieve / not suitable for deep sedation
• Main adverse effects are CV ie bradycardia & hypotension; but manageable eg avoid loading dose and high dose, reduce dose in high risk pts
• Contraindicated in bradycardia, 2nd/3rd degree heart block, shock/hypotension despite IV fluids/vasopressors, liver failure
• Doesn’t always work, need rescue medications or even discontinuation and switch (lack of efficacy ~ 1 in 8-10 pts)
Summary/Key Additional Points to Take Home

- Rousable/cooperative sedation
- Enhances ability to communicate with caregivers
- Reduces delirium; also hastens resolution of delirium
- Shortens duration of ventilation, faster extubation
- Treat and facilitates extubation in agitated delirium
- Facilitation of successful NIV in agitated pts

\[
\text{DELIRIUM} \xrightarrow{\text{DEXMEDETOMIDINE}} \text{MORTALITY + NEUROCOGNITIVE SEQUELAE} \uparrow \uparrow \\
\text{DEXMEDETOMIDINE} \xrightarrow{\text{DEXMEDETOMIDINE}} \text{DELIRIUM} \downarrow \downarrow \\
\text{DEXMEDETOMIDINE} \xrightarrow{\text{MORTALITY}} \text{COGNITIVE FX? QOL?} \uparrow \uparrow
\]

WILL “EGDS vs STANDARD CARE SEDATION” GIVE US AN ANSWER?
Depth of Sedation in MIDEX


Patients (N)

Average RASS during Trial

Dexmedetomidine
Midazolam

Average RASS
Dex –0.9 vs Midaz –1.5
p<.001

Time at “Target Sedation”
p=.15

Depth of Sedation in PRODEX

Average RASS during Trial

Dexmedetomidine
Propofol

Dex -1.0 vs Prop -1.7

\( p < .001 \)

Heart Rate and Blood Pressure Change

- Patients receiving sedative infusions and analgesics to provide comfort and pain relief. Therefore, a reduction in blood pressure and heart rate is expected with reduced anxiety, agitation and sympathetic drive.

- Dexmedetomidine is known to produce a reduction in heart rate in most patients. This occurs with doses as low as 0.1 mcg/kg/hr and is dose related to a max of 1 mcg/kg/hr. Peak effect occurs at 8 to 12 hours after initiation of dexmedetomidine.

- Most patients will have a reduction in Heart Rate (HR) that is NOT clinically relevant i.e. BP is stable and therefore may not require intervention.

- Less than 5% of patients may have a reduction in HR that may be clinically relevant i.e. HR < 55/min with a low BP and hence needs treatment.

- It takes 6 to 8 hours for the sympatholytic and bradycardia effect to recover following dexmedetomidine dose reduction or cessation of the infusion.

- Dexmedetomidine produces a bimodal effect on BP dependent on plasma concentration achieved:
  - At low dose, 0.1- around 0.7 mcg/kg/hr - produces a dose dependent reduction in BP.
  - At higher dose, greater than 0.7 mcg/kg/hr - produces a dose dependent increase in BP.

*SLIDE COURTESY OF PROF YAHYA SHEHABI*
Managing HR and BP

- HR is $< 55/min + \text{adequate BP}$ with CV stability $\rightarrow$ observe (check perfusion status).

- HR is $< 55/min + \text{borderline or low BP}$:
  - You may give atropine 300 mcg IVI to reduce possible vagal effect.
  - If no improvement within 5 min, consider a low dose dobutamine $2\text{ mcg/kg/min}$ or adrenaline $0.05\text{ mcg/kg/min}$ (Clinician’s choice).
  - Reduce Dexmedetomidine infusion by $0.2\text{ mcg/kg/hr}$. Please note the long offset time for bradycardia. Maintain RASS target as per protocol.
  - You may increase dobutamine / adrenaline to the desired effect.

- Low BP + normal HR or borderline bradycardia $=$ treat per usual with fluid boluses and/or vasopressor of choice.
  - Metaraminol $0.5\text{ mg bolus}$ for immediate temporising effect.
  - Noradrenaline infusion (0.05 mcg/kg/min for sustained effect.

*SLIDE COURTESY OF PROF YAHYA SHEHABI*
PHARMACOLOGY OF DEXMEDETOLOPIDINE

• Continuous infusion:
  ➢ Onset of action: 15 mins
  ➢ Peak concentrations within 1 hour
• Highly (94%) protein bound, free fraction 6%
• Distribution half-life: 6 mins
• Terminal half-life: 2.0 – 2.5 hrs
• Extensively metabolised in liver
• No known active metabolites
• Inactive metabolites 95% excreted in kidneys
Daily incidence of delirium after study drug initiation:
- decreased in dex group
- Increased in mida group

CV Safety:
- Dex – ↑ incidence of bradycardia (42.2% vs 18.9%) p < 0.01
  - 5 pts HR < 40
  - 4.9% (12/244) required intervention
  - No rebound HPT or tachycardia after discontinuation
- Mida – higher incidence of tachycardia
  - more hypertension requiring treatment
Conclusions – dexmedetomidine resulted in:

- Reduced development of delirium AND improved the resolution of delirium if it develops
- Shortened time on mechanical ventilation
- Earlier extubation
- Bradycardia more common with dexmedetomidine
- Tachycardia & hypertension more common with midazolam
Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation
Two Randomized Controlled Trials

• Safety:
  – PRODEX: hypotension & bradycardia rates similar
  – MIDEX: hypotension no significant difference
    bradycardia – mida 5.2%, dex 14.2% (p=0.01)

• Conclusions:
  – Dexmedetomidine not inferior to midazolam or propofol for long term (mild-moderate) sedation in ventilated ICU pts
  – Shorten ventilation compared to mida but not propofol
  – Reduce time to extubation compared to both mida & propofol
  – Enhanced ability to communicate with staff
CARDIOVASCULAR EFFECTS

The Effects of Increasing Plasma Concentrations of Dexmedetomidine in Humans

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- Healthy volunteers
- IVI dexmedetomidine to achieve increasing plasma concentrations of dexmedetomidine
- Autonomic, cardiovascular & sedative responses
Adrenergic effects of dexmedetomidine

Fig. 2. The catecholamine responses to target, controlled infusions of dexmedetomidine. Plasma levels of norepinephrine and epinephrine (mean ± SD) both decreased substantially after the first dose and remained suppressed throughout the infusion period and into the recovery period. *Significant change from preinfusion baseline value, \( P < 0.05 \).
<table>
<thead>
<tr>
<th>Other clinical outcomes</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilator-free, days (d)</td>
<td>22 (0-24)</td>
<td>18 (0-23)</td>
<td>.22</td>
</tr>
<tr>
<td>Intensive care unit length of stay, days (d)</td>
<td>7.5 (5-19)</td>
<td>9 (6-15)</td>
<td>.92</td>
</tr>
<tr>
<td>28-Day mortality, No. (%)</td>
<td>9 (17)</td>
<td>14 (27)</td>
<td>.18</td>
</tr>
</tbody>
</table>