Sedation, analgesia and neuromuscular blockade in the critically ill

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- When to sedate?
- Which agent is better?
- Any head to head comparison?
- How to monitor?
- Does sedation have an advantage, if so what?
- Disadvantages

Goals of analgesia and sedation

- Comfort and safety of the patient
- Better ventilator-patient synchrony
- To reduce the stress related to the critical illness

Distress in the critically ill

- Critically ill patients, especially intubated patients often develop agitation – pain, anxiety, unable to communicate with care-givers
- First step: correct the cause of agitation (pain relief, correction of fever, hypoxemia, etc.)
- Delirium and its risk factors – fever, dyselectrolytemia, drug withdrawal, etc. to be looked for and corrected

Distress in the critically ill

- Initial management- conservatively managing the identifiable cause of distress
- *Non-pharmacologic management*: Reassurance, interaction with the patient and reorientation, family visits, cognitive behavior therapy[1]
- *Sedation*: when these are not effective in controlling the distress

[1] Fontaine DK. Crit care Clin ; 10: 695

Sedate or not to sedate?

	No sedation (n 55)	Sedation (n 58)	p value
Mechanical ventilation free days(from intubation to day 28)	13·8 (11·0); 18·0 (0–24·1)	9·6 (10·0); 6·9 (0–20·5)	*0·0191*
Length of stay (days)			
Intensive care unit	13·1 (5·7–..)	22·8 (11·7–..)	*0·0316*
Hospital	34 (17–65)	58 (33–85)	*0·0039*
Mortality			
Intensive care unit	12 (22%)	22 (38%)	0·06
Hospital	20 (36%)	27 (47%)	0·27
Tracheostomy	16 (29%)	17 (29%)	0·98
Ventilator-associated pneumonia	6 (11%)	7 (12%)	0·85

Strom T, Martinussen T, Toft P. Lancet. 2010;375(9713):475-80

Sedate or not to sedate?

Other outcomes	No sedation arm	Sedation arm	P value
Accidental tube removal	6	7	0.69
CT/MRI brain	5	8	0.43
Re-intubation within 24h	7	11	0.37
Delirium	11 (20%)	4 (7%)	0.040
Haloperidol usage	19	8	0.010

No sedation group however received analgesia with morphine 2.5 or 5 mg PRN
1:1 nurse: patient ratio and dedicated counselor to reassure patients whenever required (May not be feasible practically)

Strom T, Martinussen T, Toft P. Lancet. 2010;375(9713):475-80

Unconventional ventilation and sedation

- Low tidal volume (≤ 6 mL/kg IBW) strategy though highly effective in decreasing mortality – its not physiological
- A meta-analysis of the two trials (the two trials as well as the meta-analysis was still underpowered) concluded – low tidal volume strategy not necessarily required increased sedation/analgesia

Wolthuis EK, et al. Critical care (London, England). 2007;11(4):R77
Neto SA et al. Intensive care medicine

Overview of sedatives

Sedatives in ICU
Agents causing sedation by their direct effect
(a)GABA agonists (GABA is one of the most important CNS inhibitory system)
(1) Benzodiazepines (diazepam, lorazepam, midazolam)
(2) Propofol
(b)Alpha 2 agonist
(1) Dexmedetomidine
Agents causing sedation as an adverse effect
(a) Antipsychotics
(1) Typical – haloperidol (2) Atypical – risperidone, olanzapine
(b) Opioids

Adapted from: Weinhouse GL et al. Anesthesiology Clin 29 (2011) 675–685

Which agent to use?

- Individualize based on patient factors
- Expected duration of ventilation
- Presence of organ failures, hypersensitivity to drugs
- Clinical pharmacology of the drug in use must be considered
  - Hypoalbuminemia
  - Drug interaction due to polypharmacy
  - Altered pharmacokinetics and dynamics – drug accumulation
- Cost and cost-effectiveness

Monitoring sedation

- **Sedation Agitation Scale (SAS)**
- **Richmond Agitation-Sedation Scale (RASS)**
- Observer's assessment of alertness/sedation scale (OAA/S)
- Ramsay sedation scale
- New Sheffield sedation scale
- Sedation Intensive Care Score (SEDIC)
- Motor Activity Assessment Score (MAAS)
- Adaption to Intensive care environment (ATICE)
- Minnesota Sedation Assessment Tool (MSAT)
- Vancouver Interaction and Calmness Scale (VICS)

Barr J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine. 2013;41(1):263-306.

RASS

Score	Term	Description
+4	Combative	Overtly combative, violant, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to *voice (>10 seconds)*
–2	Light sedation	Briefly awakens with eye opening to *voice (>10 seconds)*
–3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)
–4	Deep sedation	No response to voice, but movement or eye opening to *physical stimulation*
–5	Unarousable	No response to voice or *physical stimulation*

Sessler CN, Richmond,.Virginia U

Objective measures of monitoring sedation

- Auditory Evoked Potentials (AEP)
- Bispectral Index (BIS)
- Narcotrend Index (NI)
- Patient State Index (PSI)
- State entropy (SE)

Barr J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine. 2013;41(1):263-306.

Objective measures of monitoring sedation

- May serve as useful adjuncts, but not to be use as routine
- Benefit of using these objective tests do not add much to the subjective sedation scales
- Patients who are paralyzed, cannot be monitored with the subjective scale, hence may have a role in these

Barr J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine. 2013;41(1):263-306.

How much sedation?

- Light sedation improves outcome (RASS -2 to +1 in many studies. Varies from trial to trial)
- Shorter ICU stay and ventilation days
- Though light sedation may increase some physiologic stress, (increased catecholamine levels and oxygen consumption) may not be associated with negative clinical outcomes
- No difference in post ICU psychological outcome based on the depth of sedation

Barr J, et al. Critical care medicine. 2013;41(1):26
306.

Interruption of sedation

- Daily sedation interruption (DSI) defined as “short-term suspension, hold, discontinuation, cessation, or interruption of intravenous sedatives (continuous infusions or fixed dose bolus) and, in some cases, analgesic medications”

- To prevent drug bioaccumulation
- Awake state
- Assess whether liberation is possible or not and neurologic status

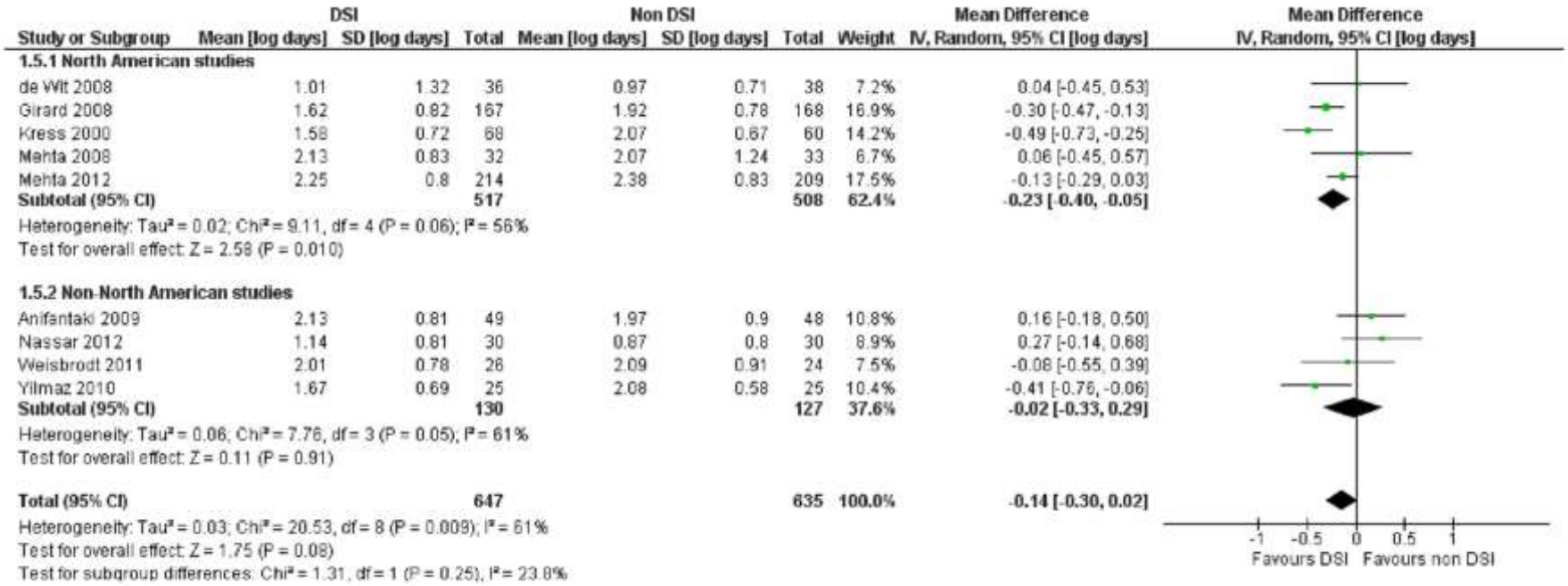
Burry L et al. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009176

Interruption of sedation

- Interruption is done till patient becomes awake, and can obey simple commands

- Daily interruption of sedation (DSI) may reduce the total duration of ventilation

Burry L et al. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009176



Total duration of ventilation was not significantly lower with DSI, but there was heterogeneity, hence subgroup analysis performed as above (I^2 = 61%)

Here north American studies showed significantly lower days o ventilator

Burry L et al. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. N
CD009176

Daily sedation interruption (DSI)

Secondary outcome	DSI vs. continuous sedation
ICU and hospital mortality	No difference noted
Length of stay, hospital and ICU	
Accidental ETT removal	
New onset delirium	
Catheter removal	
Quality of life (3/9 trials)	
Tracheostomy was performed less frequently in the DSI group (RR 0.73) reported in six trials	

Burry L et al. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. N
CD009176

Propofol

- Rapid onset and offset
- As good as midazolam and better recovery times
- Beneficial immunomodulatory effect in sepsis, SIRS

Marik PE. Pharmacotherapy. 2005;25(5 Pt 2):28s-33s
Tsuchiya M, et al. Am J of resp and crit care med. 2001;163(1):26-3

- Arterial hypotension, myocardial depression
- Hypertriglyceridemia, hyperamylasemia, bacterial contamination, propofol infusion syndrome (children, > 48h high dose infusion >5 mg/kg/h) especially in sepsis and inflammatory diseases

Propofol vs. Benzodiazepines

Data from multicenter ICU database, propensity score matching was done. Continuous sedation > 48 h were included (2003 – 2009)

Outcome	Propofol vs. midazolam	Propofol vs. lorazepam
Hospital mortality	RR 0.76	RR 0.78 (favoring propofol)
Probability of discharge at 28 d	78% vs. 69.5%	79% vs. 71.9% ($p < 0.001$)
Earlier removal from ventilator	84.4% vs. 78.1%	84.3% vs. 78.8% ($p < 0.001$)

Lonardo NW, et al. American journal of respiratory and critical care medicine. 2014;189(11):1383-94.

- Initial studies showed that time to extubation was significantly lower in propofol sedation than with midazolam
- Propofol – used in anesthesia and in post op period for short duration

- Issues were raised regarding usefulness in long and medium term sedation in ICU

Propofol for medium (>24h to 7d) and long term sedation (>7d)

- A total of 16 trials studied in a meta-analysis
  - Mortality reported in 14 trials
  - Length of ICU stay in 9 trials
  - Duration of ventilation in 4 trials
- No difference in mortality
- But significantly lesser duration of ventilation and ICU stay (In both long term and medium term usage of propofol)

Ho KM, Ng JY. Intensive care medicine. 2008;34(11):1969-79.

Delirium in propofol vs. midazolam

- Two studies (one was done in post cardiac surgery patients)
- Found no difference in delirium in both these groups

Ruokonen E,et al.Intensive Care Med2009; 35:282–290
Maldonado JR, et al. Psychosomatics2009; 50:206–217
Barr J, et al. Critical care medicine. 2013;41(1):263-306.

Dexmedetomidine

- Alpha 2 adrenergic agonist
- Similar to clonidine, but more specific
- Does not act on GABA receptors
- Acts on locus ceruleus
- No respiratory depression

Dexmedetomidine

- Recent meta-analysis: 28 studies (27 publications)
- Trials in general ICU setting – 13
- Loading dose 1 mcg/kg followed by infusion ranging from 0.1 to 2.5 mcg/kg have been in used in majority (18 trials)
- Six different comparators: propofol in 11 study, midazolam in 10, placebo in 5, morphine in 2, haloperidol and lorazepam in one each

Pasin L, et al. PloS one. 2013;8(12):e82913

Dexmedetomidine

Outcome in ICU patients		Number of trials	Dexmeditomidine vs. placebo/control
(a)Length of ICU stay in various categories	Long term sedation	6	< 0.001
	Short term sedation	11	< 0.001
	Daily interruption	5	< 0.001
	High maintenance dose	7	< 0.001
	Low maintenance dose (< 0.7 µg/kg/hr)	10	< 0.001
	Loading dose	11	< 0.001
	Loading dose and high maintenance dose	2	0.12

Adapted from: Pasin L, et al. PloS one. 2013;8(12):e82913 (table showing outcomes for only ICU related studies

Dexmedetomidine

Secondary Outcomes	Dexmed vs. control	P value (Relative risk)
Mortality	200/1499 (13%) vs. 173/1409 (12%)	0.9 (RR 1)
Hypotension	424/1389 (31%) vs. 279/1266 (22%)	0.052 (RR 1.27)
Bradycardia	220/1374 (61%) vs. 64/1246 (5%)	< 0.001 (RR 2.43)
Rescue medications: Analgesics/ Sedatives	892/1459 (61%) vs. 977/1366 (72%)	< 0.001 (RR 0.80)
Completely comfortable patients	12/253 (51%) vs. 103/254 (40.6%)	0.9 (RR 1.07)

Adapted from: Pasin L, et al. PloS one. 2013;8(12):e82913 (table showing outcomes for only ICU related studies

Adverse effects

- Decreases sympathetic activity – may increase adverse cardiac events
- Especially in individuals with autonomic disturbance, elderly, diabetics, chronic hypertension. Valvular heart disease, heart blocks, severe CAD, hypotension/ hypovolemia

Gertler R, Brown HC, Mitchell DH, et al (2001). Proc (Bayl Univ Med Cent) 14: 13–21

Other agents for sedation

- Ketamine (adv in head injury patients)
- Has been used mainly for procedural sedation and analgesia
- Not rigorously studied as an agent for sedation in critically ill
- No cardiorespiratory depression offers an advantage
- Successfully used in five pediatric patients who had cardiorespiratory depression with opioids and conventional sedatives

Tobias JD, Martin LD, Wetzel RC. Critical care medicine. 1990;18(8):819-21.

Other agents for sedation

- Sevoflurane vs. propofol/midazolam
  - Study in 60 patients (RCT)
  - All patients received remifentanil for pain up to 96 h
  - Wake up time and time to extubation was significantly better with sevoflurane (18.6 mts to 33.6 mts mean)

- Midazolam vs. isoflurane studied earlier (<24 h sedation) shorter ventilation period and early extubation

Mesnil M, et al. Intensive care medicine. 2011;37(6) 41.

Kong KL et al. BMJ 1989; 298:1277-1280
Spencer EM et al.Intensive care Med. 1992;18:415

Benzodiazepine vs. non benzodiazepine sedation

Outcome	n (trials) (follow-up)	Benefit with non BDZ
ICU length of stay	1235 (6) (45 d f/u)	-1.64 d
Duration of mechanical ventilation	1101 (4) (45 d f/u)	-1.87 d
Mortality	1101 (4) (45 d f/u)	1.01
Delirium	469 (2) (during ICU stay only)	0.82

Fraser GL, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Critical care medicine. 2013;41(9 Suppl 1):S30-8.

Benzodiazepine vs. non benzodiazepine sedation

- Thirteen trials analyzed and only six high quality studies included in another meta analysis
- ICU length of stay shortened approximately by 0.5 days (non BDZ arm)
- No mortality difference noted
- Overall conclusion: Non BDZ modestly effective in reducing ICU LOS than BDZ sedation

Barr J, et al. Critical care medicine. 2013;41(1):263-306.

Disadvantages of sedation

- Prolonged hospital stay
- Prolonged weaning and ICU stay
- Increased risk of ICU acquired infections (immunomodulatory effects of sedatives, microaspiration etc,) Nseir et al. Crit Care.2010.14:R30
- Risk of delirium
- Cost and cost of hospitalisation
- Distorted sleep architecture. BDZ reduce slow wave sleep, dexmedetomidine causes distortion (but not noted to have clinical benefit)

Weinhouse LG. Anesthesiology Clin.2011; 29:675

Interpret with caution

- Almost all trials exclude <18 years of age
- Significant renal and liver failure patients were excluded in many studies

Ho KM, Ng JY. Intensive care medicine. 2008;34(11):1969-79.

- Long term effect of these sedatives are not known
- Propofol and midazolam can have long term effect on cognitive function

Perouansky M (2007). Eur J Anaesthesiol 24:107–11

Absolute cost vs. cost effectiveness

- Non benzodiazepine based regimens absolute cost is more than benzodiazepine based regimens, but overall effectiveness is better with non benzodiazepine regimens

Bioc JJ, et al. Journal of critical care. 2014;29(5):753-7.

Analgesia

- Pain is a significant problem. Up to 82% ICU discharged patients remembered pain due to ETT

. Rotondi AJ, et al: Crit Care Med2002; 30:746–752

- Patients with pain in ICU are at high risk of post traumatic stress disorder, poor quality of life and are likely to suffer from chronic pain

Schelling G, et al: Crit Care Med1998; 26:651–659

- Pain assessment by Behavioural Pain Scale (BPS) and Critical-Care Pain Observation Tool (CPOT)

Barr J, et al. Critical care medicine. 2013;41(1):263-306.

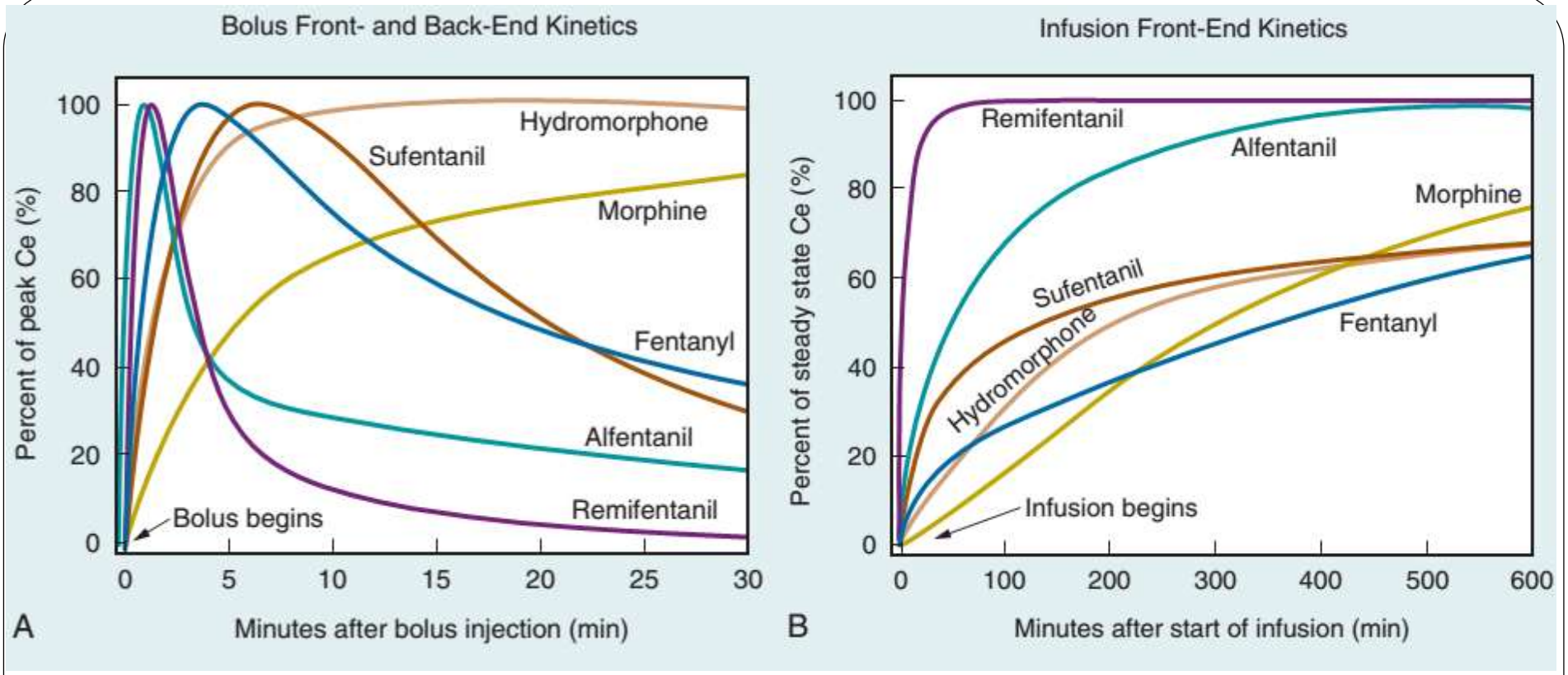
- Routine pain assessment by valid scales enable reduction in analgesic dose
- Length of ICU stay and duration of ventilation are also reduced

Payen JF, al; DOLOREA study. Anesthesiology2009; 111:1308–1316
Payen JF, et al: Anesthesiology2007; 106:687–695; quiz 891

Agent	Analgesic Dose (IV)	Half-Life	Metabolic Pathway	Active Metabolites (Effect)	Adverse Effects	Intermittent Dose*	Infusion Dose Range (Usual)
Fentanyl	200 µg	1.5–6 hr	Oxidation	No metabolite, parent accumulates	Rigidity with high doses	0.35–1.5 µg/kg IV q0.5–1h	0.7–10 µg/kg/hr
Hydro morphone	1.5 mg	2–3 hr	Glucuronidation	None	—	10–30 µg/kg IV q1–2h	7–15 µg/kg/hr
Morphine	10 mg	3–7 hr	Glucuronidation	Yes (sedation, especially in renal insufficiency)	Histamine release	0.01–0.15 mg/kg IV q1–2h	0.07–0.5 mg/kg/hr
Meperidine	75–100 mg	3–4 hr	Demethylation and hydroxylation	Yes (neuroexcitation, especially in renal insufficiency or high doses)	Avoid with MAOIs and SSRIs	Not recommended	Not recommended
Codeine	120 mg	3 hr	Demethylation and glucuronidation	Yes (analgesia, sedation)	Lacks potency, histamine release	Not recommended	Not recommended
Remifentanil	—	3–10 min	Plasma esterase	None	—	—	0.6–15 µg/kg/hr
Ketorolac	—	2.4–8.6 hr	Renal	None	Risk of bleeding, GI and renal adverse effects	15–30 mg IV q6h, decrease if age >65 yr or weight <50 kg or renal impair-ment, avoid >5 days use	
Ibuprofen	—	1.8–2.5 hr	Oxidation	None	Risk of bleeding, GI and renal adverse effects	400 mg PO q4–6h	—
Acetamin-ophen	—	2 hr	Conjugation	—	—	325–650 mg PO q4–6h, avoid >4 g/day	—

- Drug of choice – opioids
- Morphine avoided in renal failure as its active metabolite accumulates
- Fentanyl is hence used
- All opioids similar efficacy and outcomes when the same degree of analgesia is achieved
- Neuropathic pain – add gabapentin, carbamazepine
- Non-opioids – adjuncts, serve to reduce opioid
- No direct comparison of opioids vs. non-opioids

Barr J, et al. Critical care medicine. 2013;41(1):263-306



Lotsch J.Clin Pharmacol Ther. 2002;72:151-162.

Lotsch J, et al. Anesthesiology. 2001;95:1329-1338.

Drover DR, et al. Anesthesiology. 2002;97:827-836.

Hill JL et al.Psychopharmacology (Berl). 2000;152:31-39.

Hudson RJ, et al. Anesthesiology. 1989; 70:426-43

Adapted from: Ogura T, Egan TD. Opioid agonists and antagonists. Chap 15 clinical pharmacology

Analgosedation

- Manage discomfort and pain first
- Sedation to be considered subsequently
- Remifentanil has been used
- Titration is easy, metabolism is not dependent on renal/liver functions
- Nine trials (remifentanil analgosedation vs. midazolam, propofol, fentanyl, morphine)
- Shorter duration of ventilation, ICU stay and early weaning

Devabhakthuni S, Aet al. The Annals of pharmacotherapy. 2012;46(4):530-40.

Neuromuscular blocking agents (NMBAs)

Classification of NMBAs – depolarising agents

- Succinylcholine

Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonist. Miller's anesthesia. Chap 29; 859-911.

Classification of NMBAs – non depolarising agents

Class of Blocker	Clinical Duration			
	Long-Acting (>50 min)	Intermediate-Acting (20-50 min)	Short-Acting (15-20 min)	Ultrashort-acting (<10-12 min)
Steroidal compounds	Pancuronium Pipecuronium	Vecuronium Rocuronium		
Benzylisoquinolinium compounds	*d*-Tubocurarine Metocurine Doxacurium	Atracurium Cisatracurium	Mivacurium	
Others				
Asymmetrical mixed-onium chlorofumarates				Gantacurium
Phenolic ether	Gallamine			
Diallyl derivative of toxiferine	Alcuronium			

A majority of nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. *d*-Tubocurarine, vecuronium, rocuronium, and rapacuronium are monoquaternary compounds, and gallamine is a trisquaternary ammonium compound.

Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonist. Miller's anesthesia. Chap 29; 859-911.

Indications for NMBAs

- Intubation
- Facilitation of mechanical ventilation
  - Non-conventional ventilatory strategies (35%)
  - Hypoxemia (25%)
  - Reduced lung compliance (25%)
  - Ventilator-patient dys-synchrony (18%)
  - Permissive hypercapnia (15%)
  - Prone position ventilation
- Less commonly: to reduce metabolic demands, agitation and in raised intracranial pressure

Arroliga A et al. Chest. 2005;128(2):496-506.
Price D, Kenyon NJ, Stollenwerk N. Annals of intensive care. 2012;2(1):43.

Indications for NMBAs during MV

Reason	Odd's Ratio
Permissive hypercapnia	4.49
Prone position	4.36
Full ventilatory support	3.68
PEEP ≥ 10 cmH2O	3.06
Plateau pressure > 35 cmH2O	2.19

Arroliga A et al. Chest. 2005;128(2):496-506.

Which agent to use?

- Succinylcholine for RSI and short term usage
- Many side effects: raised ICP, IOP, malignant hyperthermia, hyperkalemia, bradyarrhythmias
- For ARDS, trials are done with continuous cis-atracurium infusin
- None of the other agents have been systematically studied

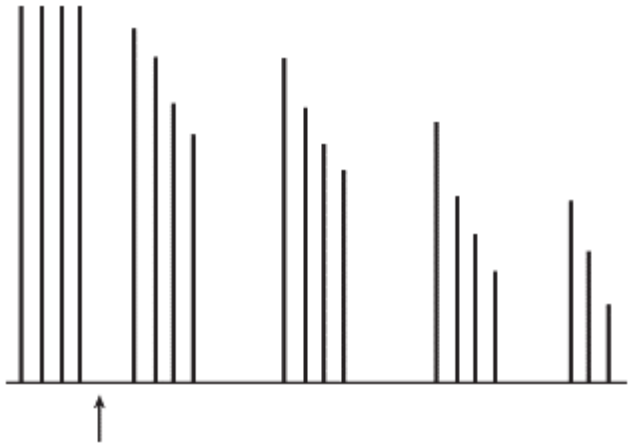
Which agent to use?

- Normal hepatic renal function – pancuronium (>1h if required)
- Cardiovascular disease – vecuronium (least cardiovascular side effects)
- Hepatic and or renal dysfunction – atracurium/cisatracurium (hoffmann elimination)

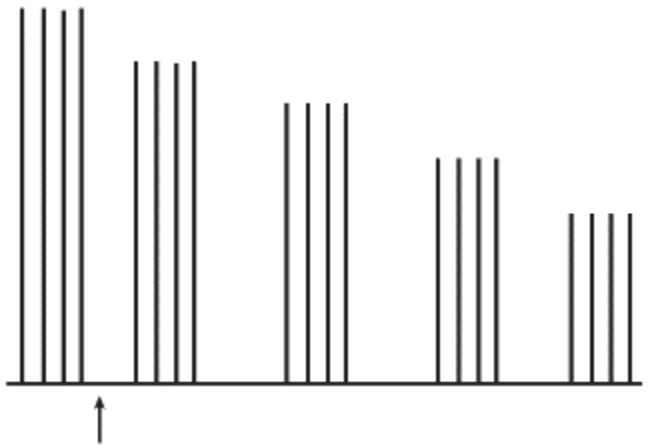
Elliot JM et al. Acta Anaesthesiol Scand suppl 1995;106:70
Hunter JM. N Engl J Med 1995;332:1691

Monitoring of NMBAs

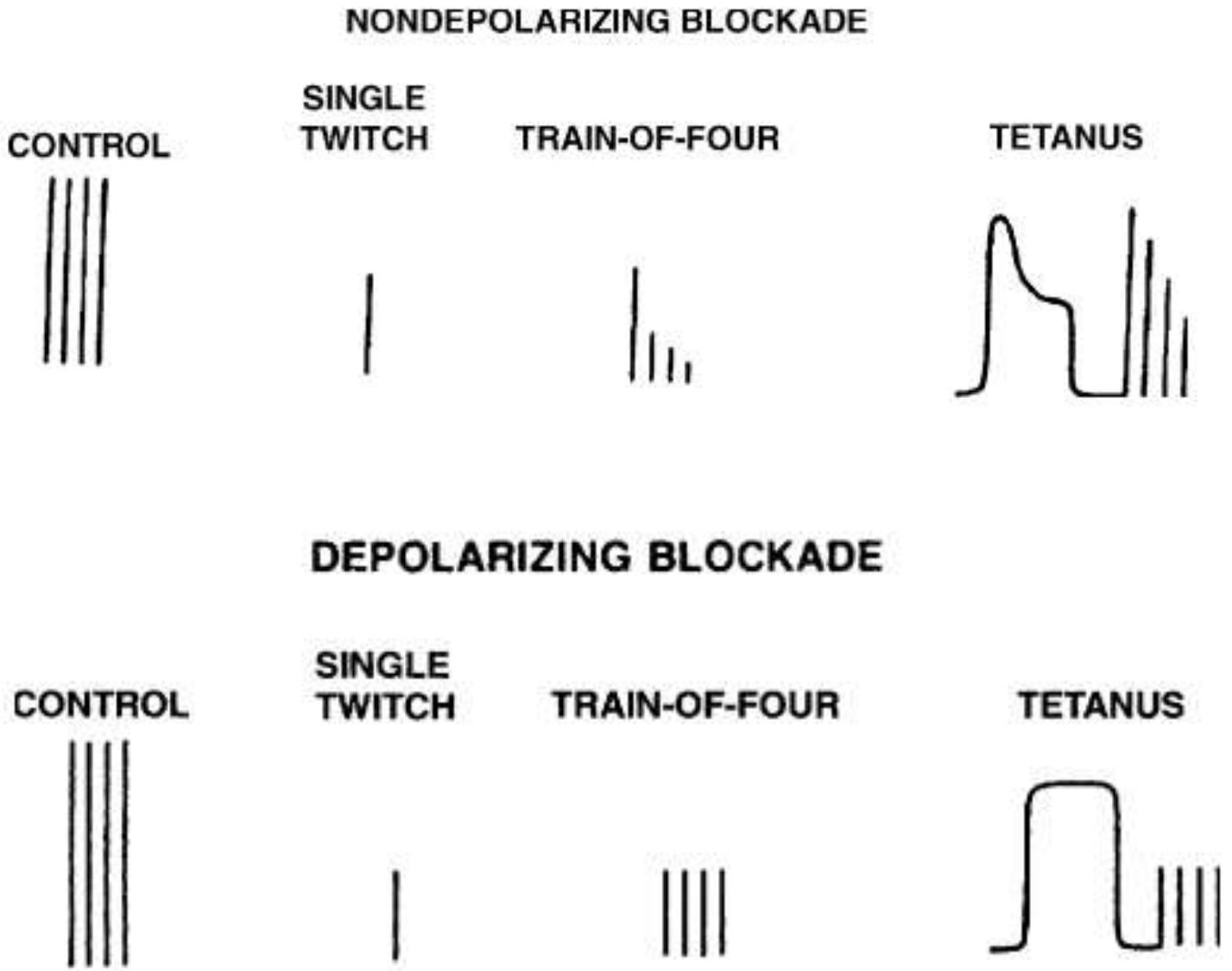
- Monitoring is recommended for all patients
- Train of four (TOF) responses in the abductor pollicis muscle after stimulation of the ulnar nerve
- Four stimuli are applied over a 2 sec period, each lasting 0.5 s



Non/partial depolarizing muscular blockers



Depolarizing muscular blockade with succinylcholine



Bevan DR, Bevan JC, Donati F:Muscle relaxants in clinical anesthesia, Chicago, 1988, Year Book, pp 49–70

Beneficial effects NMBA in ARDS

Reference	Methods	Outcome	Results
Gainnier M et al. Critical care medicine. 2004;32(1):113-9.	Multicenter, randomized Four ICUs: (n -56) med/med surg mixed PaO2/fiO2 150, PEEP ≥ 5 cmH2O ACMV Conv vs. 48h cisatracurium infusion	Gas exchange over 120 hr period	48, 96 and 120 h after randomization PaO2/fiO2 was better in the NMBA group
Forel JM et al. Critical care medicine. 2006;34(11):2749-57.	Multicenter, randomized (n -36) 1 med and 2 med surg ICU PaO2/fiO2 200, PEEP ≥ 5 cmH2O	Pulmonary and systemic inflammation – as assessed by BAL and serum TNF, IL-1, IL-6, IL-8 at pre randomization and	Significantly lower proinflammatory markers in NMBA group Improved PaO2/fiO2 in the

Beneficial effects NMBA in ARDS

Reference	Methods	Outcome	Results
Papazian L et al. The New England journal of medicine. 2010;363(12):1107-16.	Multicenter, double bind, randomized 20 ICUs: (n -340) med/med surg mixed PaO2/fiO2 150, PEEP ≥ 5 cmH2O ACMV Conv vs. conv with 48h cisatracurium infusion	Mortality in hospital Mortality at 90 d of enrollment into the study	Mortality benefit at 28 and 90 d No increase in ICU paresis Pneumothorax (11.7% vs. 4% p 0.01)

Outcome assessed	Included trials (4)	Results (p value of NMBA vs. conv)
Hospital mortality	(1),(2),(3)	RR 0.72 (p 0.005)
ICU mortality	(1),(2),(3)	RR 0.70 (p 0.004)
28 day mortality	(1),(2),(3)	RR 0.66 (p 0.003)
Days free of MV	(1),(2),(3)	MD 1.91 (p 0.002)
Total duration of MV	(1),(2),(3)	MD 1.21 (p 0.43)
ICU acquired weakness	(1),(2),(3)	RR 1.08 (p 0.57)
ICU stay	(1)	RR 1.80 (p 0.38)

MV- Mechanical ventilation, MD mean difference, RR- relative risk

(1)Gainnier M et al. Critical care medicine. 2004;32(1):113-9
(2) Forel JM et al. Critical care medicine. 2006;34(11):2749-57
(3) Papazian L et al. The New England journal of medicine. 2010;363(12):1107-16
(4)Alhazzani W et al.Critical care (London, England). 2013;17(2):R43.

Criticisms of ACURASYS trial

- Crude 90 d mortality 31.6% in NMBA group and 40.7% in placebo arm, p value 0.08
- After adjustment for baseline paO_2:fiO_2, plateau pressure and SAPS II score, the 90 d mortality rate was significantly better in the NMBA arm (p 0.04)
- Only in-hospital 90 d mortality rate assessed. All those who been randomized should have been followed up
- Muscle weakness assessed at 28 d (and no long term data)

Yegneswaran B, Murugan R. Critical care (London, England). 2011;15(5):311.

Beneficial effects

- Improvement in oxygenation
- Reduction in inflammatory response
- Mortality benefit
- Reduced risk of barotrauma

ICU acquired weakness

- Critical illness polyneuropathy/myopathy (CIP/CIM)
- Incidence in ARDS is up to 34% - 60%
- Risk factors : hyperglycemia, immobilisation (as with NMBA), corticosteroid therapy, multiple organ dysfunction (>2), and prolonged mechanical ventilation
- CIP/CIM is higher with steroidal agents (vecuronium) is much higher than that with atracurium/cisatracurium

Latrocino N et al. Lancet neurol 2011; 10: 931-941

Interventions to prevent CIP/CIM

- Many have been tried
- Nutritional supplement (arginine,glutamine)
- Antioxidant therapy
- Testosterone
- Electrical muscle stimulation
- Early mobilization and rehabilitation
- Electrical muscle stimulatiom
- Control of hyperglycemia (intensive insulin therapy)

Hermans G et al. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD006832.

Interventions to prevent CIP/CIM

- Intensive insulin therapy (2 large trials) reduces ICU stay, duration of ventilation and 180 d mortality (but significantly more hypoglycemias)
- Early rehabilitation potentially beneficial (modest evidence)
- Other interventions do not have adequate data to support it

Hermans G et al. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD006832.

Anaphylaxis

- Known with atracurium (hypotension, flushing and bronchospasm 0.2% each)

- Reports of cisatracurium causing anaphylaxis are also available (none encountered in the large trials)

Yoon Y. Korean J of Anesthesiol. 2013 Aug; 65: 147-150

- Complete blinding is not possible in these trials
- No controlled trials on other NMBAs
- The studies (all three) on cis-atracurium have been done by the same group of investigators
- No head to head comparison among various NMBAs
- Hence data needs cautious interpretation
- As per current evidence

SUMMARY

- The cause for agitation should be sought and corrected whenever feasible
- Pain, especially with suctioning, position change and immobility contributes to agitation
- Adequate analgesia to be ensured before sedation is considered
- Effectively managing these factors along with pain relief can be as effective as continuous sedation (low quality evidence, one RCT from a single center)

SUMMARY

- The requirement for sedation should be individiualized
- Short term sedation (<24 h): non benzodiazepine regimens are preferred, dexmedetomidine, propofol over benzodiazepines
- Medium and long duration (< 7 and > 7 d): Benzodiazepines are the time tested drugs, especially long acting lorazepam. Current evidence however supports non benzodiazepine regimens

SUMMARY

- Shorter days on ventilator has been consistently seen with non benzodiazepine regimen, whereas some studies suggest a shorter ICU stay as well
- No significant difference with regards to mortality and delirium with these two regimen
- Daily sedation interruption with awake trial and light sedation during the rest of the time are recommended

SUMMARY

- Benzodiazepines still play an important role in treating drug/alcohol withdrawal, seizures and anxiety.
- Monitoring of sedation with either RASS or SAS to be done 2 – 4 hrly
- Analgosedation with remifentanil based regimens may replace the sedative-hypnotic regimen in future, however currently combination of analgesic (opioid + BDZ/non BDZ sedative) is a reasonable option

SUMMARY

- Cisatracurium effective when used in first 48h in severe ARDS patient (<150 or even <120 paO_2/FiO_2 with PEEP > 5 cmH_2O)
- Other NMBAs vecuronium may be used if intermittent paralysis is required (Cisatracurium short acting hence requires infusion)
- Judicious use of steroids, NMBA coupled with early rehabilitation and blood sugar control required

Cost

	Dose	Price	Usual dosage
Midazolam	1 mg/mL	10 mL : Rs/55	0.02-0.1 mg/kg/hour
Lorazepam	2 mg /mL	2 ml X 5: Rs/75	0.01-0.1mg/kg/hour
Propofol	1%	50 mL : Rs/368	0.3 mg/kg/h
Dexmedetidomidine		200 mg Rs/558	1 mcg loading f/b 0.2 – 0.7 mcg/kg/h
Fentanyl	50 mcg/mL	10 mL: Rs/126	0.7-10 mcg/kg/h
Remifentanil			0.1 mcg/kg/h initial
Cisatracurium			0.5-10 mcg/kg/mt
Vecuronium	10 mg vial	Rs/227	0.8-1.7 mcg/kg/mt