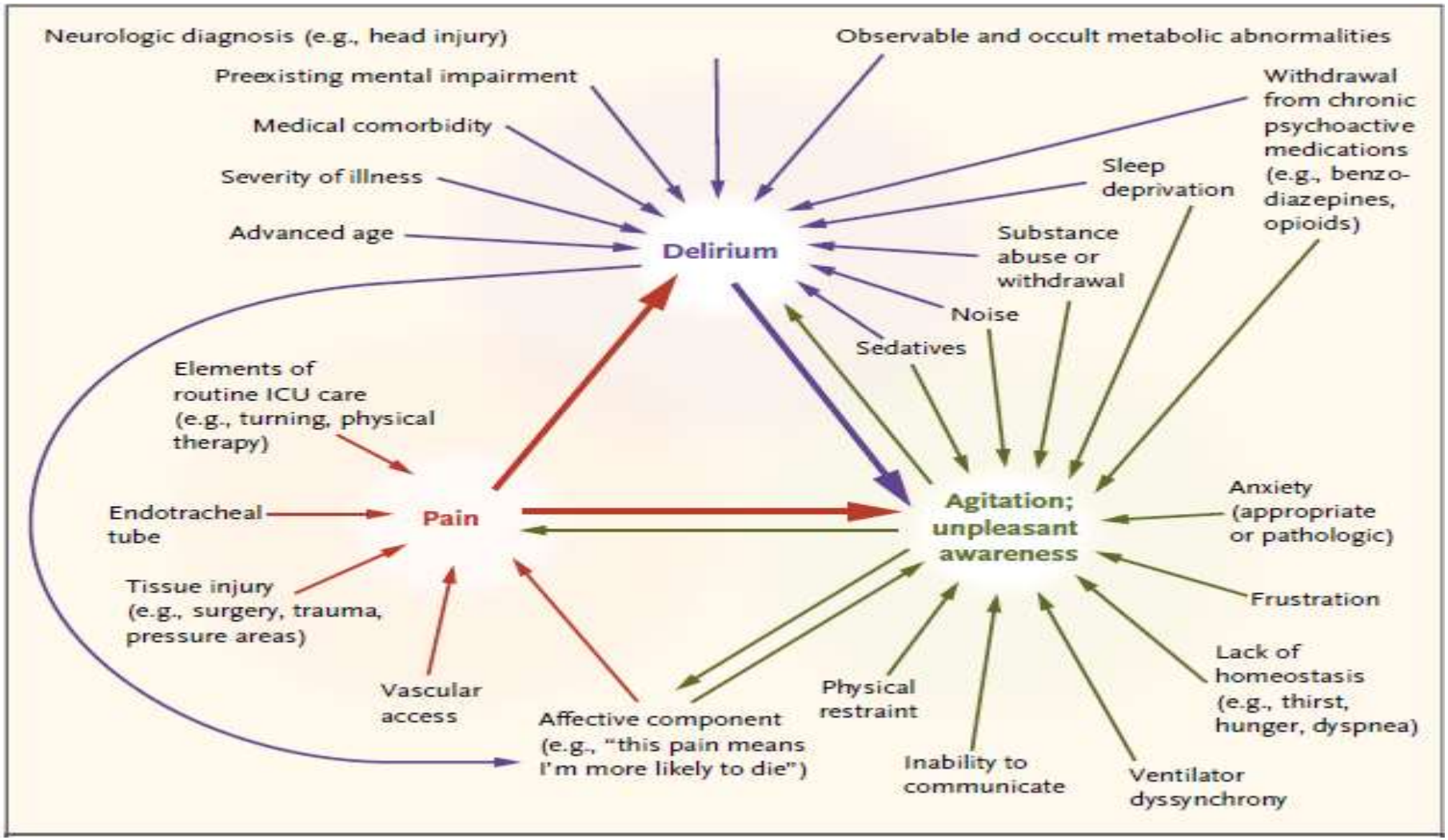
Agents and protocols for sedation-analgesia in critically ill patients

Dr. Selva Vijay S

Objectives

- ICU triad
- Pain in ICU – Assessment and agents available
- Sedation – Evolution of sedation practice in ICU
- Comprehensive evidence for agents used in ICU
- Analgo-sedation concept
- Sedation monitoring
- Brief summary

ICU triad



Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444-54.

How presentation of pain differs in a ICU patient?

- ICU patients are often mechanically ventilated and hence self-reporting of pain is not possible
- This warrants ICU physician to pick up the signs which signals discomfort to the patient. Hence the importance of pain management protocols in ICU
- Uncontrolled pain may lead to prolonged mechanical ventilation, increased ICU length of stay, pulmonary complications, patient–ventilator asynchrony, post-traumatic disorder
- The over-treatment of pain may lead to prolonged mechanical ventilation, prolonged cognitive impairment, delirium, respiratory depression, hemodynamic impairment etc

John W Devlin et al, Crit Care Med. 2018;46(9):e825-e873.
Pota, V *et al.* Pain in Intensive Care: A Narrative Review. *Pain Ther: 2022* (**11);** 359–367.

List of procedures associated with pain in ICU

- Arterial line insertion
- Peripheral IV insertion
- Central line insertion
- Peripheral blood draw
- Femoral sheet removal
- Respiratory exercises
- Mouth care
- Eye care
- Mobilization
- Nasogastric tube insertion
- Nursing care (Sheet-change, repositioning)
- Extubation

How to assess pain in critically ill patients?

Self-report scales

- Visual analog scale – horizontal
- Visual analog scale – vertical
- Numerical rating scale – oral
- Numerical rating scale – visual
- Verbal descriptor scale
- Faces pain thermometer scale

Behavioural assessment tools

- Behavioural pain scale in intubated and non-intubated
- Critical care pain observation tool
- FACES scale
- Facial Action Coding System
- Pain in Advanced Dementia (PAINAD)
- Behavior Pain Assessment (BPAT)

- Vital signs are just clues to consider pain in critically ill patients. They are not indicators of pain in patient.
- In situation of comatose patients, behavioural assessment tools may not be possible to apply.

Behavioral Pain Scale (BPS) Tool

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

Gomarverdi S et al, Comparison of Two Pain Scales: Behavioral Pain Scale and Critical-care Pain Observation Tool During Invasive and Noninvasive Procedures in Intensive Care Unit-admitted Patients. Iran J Nurs Midwifery Res. 2019 Mar-Apr;24(2):151-155

Critical care pain observation tool

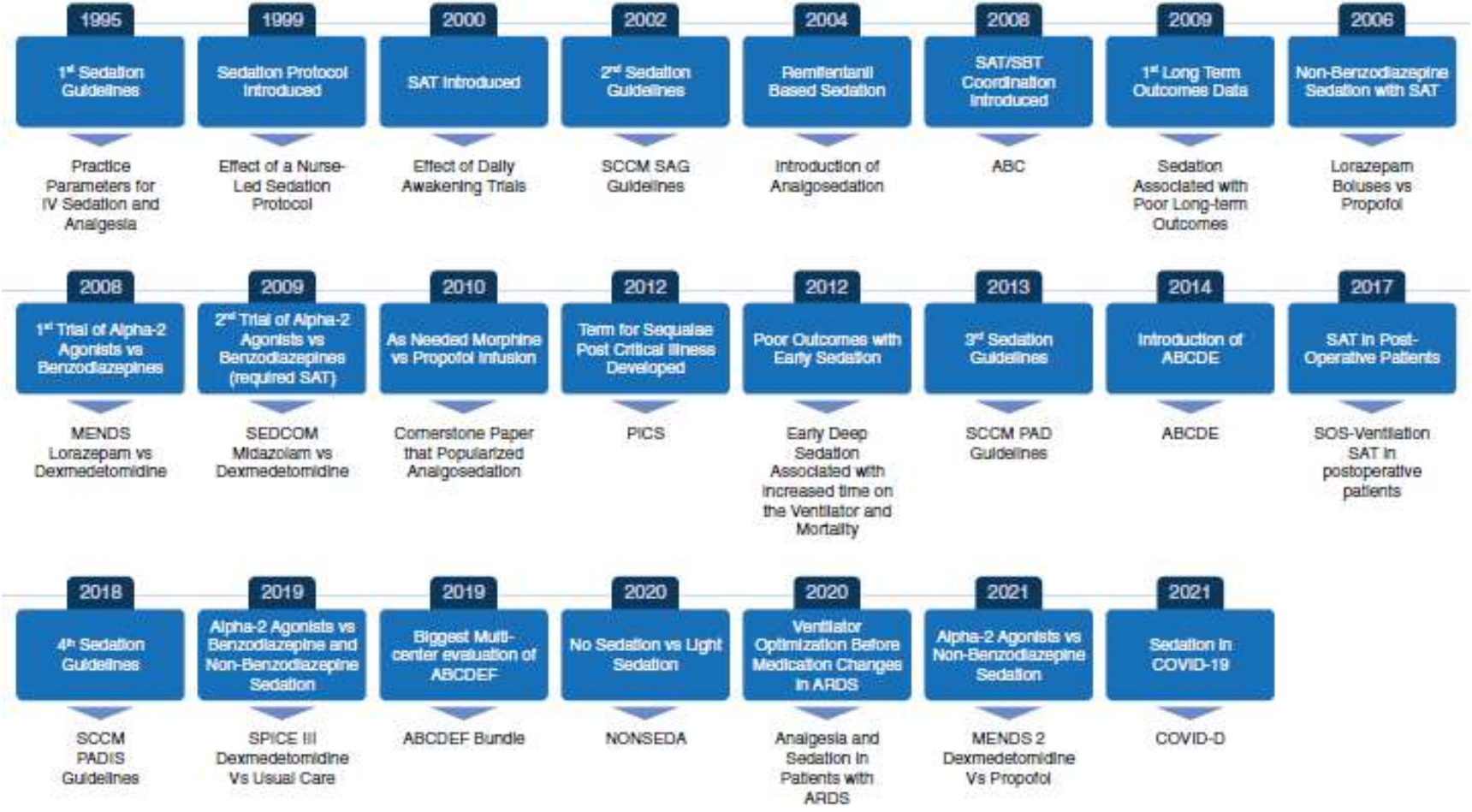
Indicator		Description	Score
Facial expression	Relaxed, neutral	No muscle tension observed	0
	Tense	Presence of frowning, orbit tightening, levator contraction, or any other change (e.g., opening eyes or tearing during nociceptive procedures	1
	Grimacing	All previous facial movements plus eyelid tightly closed	2
Body movements	Absence of movements or normal position	Does not move at all or normal position (movements not aimed toward the pain site)	0
	Protection	Slow, cautious movements, touching, or rubbing the pain site, seeking attention through movements	1
	Restlessness	Pulling tube, attempting to sit up, moving limbs, not following commands, trying to climb out of bed	2
Compliance with the ventilator (intubated patient)or Vocalization (nonintubated patient)	Tolerating ventilator or movement	Alarms not activated, easy ventilation	0
	Coughing but tolerating	Coughing, alarms may be activated	1
	Fighting ventilator	Asynchrony: blocking ventilation, alarms frequently activated	2
	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Muscle tension Evaluation by passive flexion and extension of upper limbs (in rest or when patient is being turned)	Relaxed	No resistance to passive movements	0
	Tense, rigid	resistance to passive movements	1
	Very tense or rigid	Strong resistance to passive movements, inability to complete them	2
Total			-/8

Need of sedation in ICU

- Reduce anxiety, pain and agitation
- Facilitate smooth ICU therapy (invasive procedure, mechanical ventilation)

Upadhyay, Surjya & Tripathy et al, A Practical Guide To Sedation And Analgesia In Paediatric Intensive Care Unit (Icu). Journal Of Anesthesia And Surgery. 2017: 4; 1-6

Evolution of sedation practice in ICU



Stollings, J.L. et al, Evolution of sedation management in the intensive care unit (ICU). Intensive Care Med 2022;48:1625–28.

DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

JOHN P. KRESS, M.D., ANNE S. POHLMAN, R.N., MICHAEL F. O'CONNOR, M.D., AND JESSE B. HALL, M.D.

Duration of mechanical ventilation	• 2 days lower in the sedation interruption group • 4.9 days vs 7.3 days (p- 0.004)
Median length of stay in ICU	• 3.5 days lower in the intervention group • 6.4 days vs 9.9 days (p – 0.02)
Investigations	• Facilitated neurological examination • 16 vs 6 imaging investigations • Reduced unnecessary investigations
Cost	• Reduced cumulative dose of sedatives • Cost benefit

Kress JP et al, Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000 May 18;342(20):1471-7

What we do not know?

- Sub-group analysis outcome (ARDS, COPD, Asthma, Cardiogenic shock)
- How many patients were receiving paralytic agent and what is the response in them

Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

Timothy D Girard, John P Kress, Barry D Fuchs, Jason W W Thomason, William D Schweickert, Brenda T Pun, Darren B Taichman, Jan G Dunn, Anne S Pohlman, Paul A Kinniry, James C Jackson, Angelo E Canonico, Richard W Light, Ayumi K Shintani, Jennifer L Thompson, Sharon M Gordon, Jesse B Hall, Robert S Dittus, Gordon R Bernard, E Wesley Ely

- Breathing without assistance was 3.1 days earlier in the SAT f/b SBT group
- Reduced ICU stay and hospital stay (3.7 days earlier) in the SAT f/b SBT group
- Duration of coma (2 vs 3 days, p – 0.002) in the SAT group
- Total re-intubation and tracheostomy rates were similar
- No mortality benefit (28 days mortality benefit)
- Duration of delirum is similar

SAT – spontaneous awakening trials
Daily interruption of sedations

Girard TD et al, Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008 Jan 12;371(9607):126-34.

Who did not undergo SAT? (Whom should be avoided?)

- Active seizures
- Alcohol withdrawal
- Sedation dose on escalating trend due to agitation
- NMBA
- MI in previous 24 hours
- Raised ICT

Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

William D Schweickert, Mark C Pohlman, Anne S Pohlman, Celerina Nigos, Amy J Pawlik, Cheryl L Esbrook, Linda Spears, Megan Miller, Mietka Franczyk, Deanna Deprizio, Gregory A Schmidt, Amy Bowman, Rhonda Barr, Kathryn E McCallister, Jesse B Hall, John P Kress

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

***Table 3:* Main outcomes according to study group**

Schweickert WD et al, Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009 May 30;373(9678):1874-82

	Intervention (n=49)	Control (n=55)	p value
Time from intubation to first PT/OT session (days)	1·5 (1·0–2·1)	7·4 (6·0–10·9)	<0·0001
Independent ADLs total at ICU discharge	3 (0–5)	0 (0–5)	0·15
Independent ADLs total at hospital discharge	6 (0–6)	4 (0–6)	0·06
MRC examination score at hospital discharge	52 (25–58)	48 (0–58)	0·38
Hand-grip strength at hospital discharge (kg-force)	39 (10–58)	35 (0–57)	0·67
Greatest walking distance at hospital discharge (m)	33·4 (0–91·4)	0 (0–30·4)	0·004
Time from intubation to milestones achieved (days)			
Out of bed	1·7 (1·1–3·0)	6·6 (4·2–8·3)	<0·0001
Standing	3·2 (1·5–5·6)	6·0 (4·5–8·9)	<0·0001
Marching in place	3·3 (1·6–5·8)	6·2 (4·6–9·6)	<0·0001
Transferring to a chair	3·1 (1·8–4·5	6·2 (4·5–8·4)	<0·0001
Walking	3·8 (1·9–5·8)	7·3 (4·9–9·6)	<0·0001

Data are median (IQR). ADLs=activities of daily living. ICU=intensive care unit. MRC=Medical Research Council. PT/OT=physical therapy and occupational therapy. MRC examination scale 0–60.

Table 4: **Function and muscle strength outcomes according to study group**

What do we get?

- OTPT may be facilitating in achieving good functional and psychological outcome
- No mortality benefit but OTPT does reduces ICU related atrophy (although no significant difference noted, a higher sample size would show a difference)

ABCDEF bundle of care

- A – assessment, prevent and manage pain
- B – Both spontaneous awakening and spontaneous breathing trials
- C – Choice of analgesia and sedation
- D – Assess, prevent and manage delirium
- E – Early mobility and exercise
- F – Family engagement

Moraes FDS et al, ABCDE and ABCDEF care bundles: A systematic review of the implementation process in intensive care units. Medicine (Baltimore). 2022 Jun 24;101(25):e29499

ABCDE and ABCDEF care bundles

A systematic review of the implementation process in intensive care units

Fabio da Silva Moraes, PhD*, Lívia Luize Marengo, PhD, Mariana Del Grossi Moura, PhD, Cristiane de Cássia Bergamaschi, PhD, Fernando de Sá Del Fiol, PhD, Luciane Cruz Lopes, PhD, Marcus Tolentino Silva, PhD, Silvio Barberato-Filho, PhD

- Meta-analysis of 20 studies
- 8 outcomes were analysed
- Also addressed the barriers and facilitators in implementation of ABCDEF care bundles in ICU practice

Primary outcomes:

- Length of stay in the ICU
- Mechanical ventilation time
- Incidence and prevalence of delirium or coma
- Level of agitation and sedation Early mobilization

Secondary outcomes:

- Mortality in the ICU and hospital Hospital length of stay
- Change in perception, attitude or behavior of the stakeholders
- Change in knowledge of health professionals

Outcomes	Significant if any
ICU length of stay	Not significant
Mechanical ventilation time	Not significant
Delirium	Decreased incidence
Coma	Not significant
Early mobilization	Increased incidence
ICU mortality	Morality benefit
Hospital length of stay	Not significant
Hospital mortality	Not significant

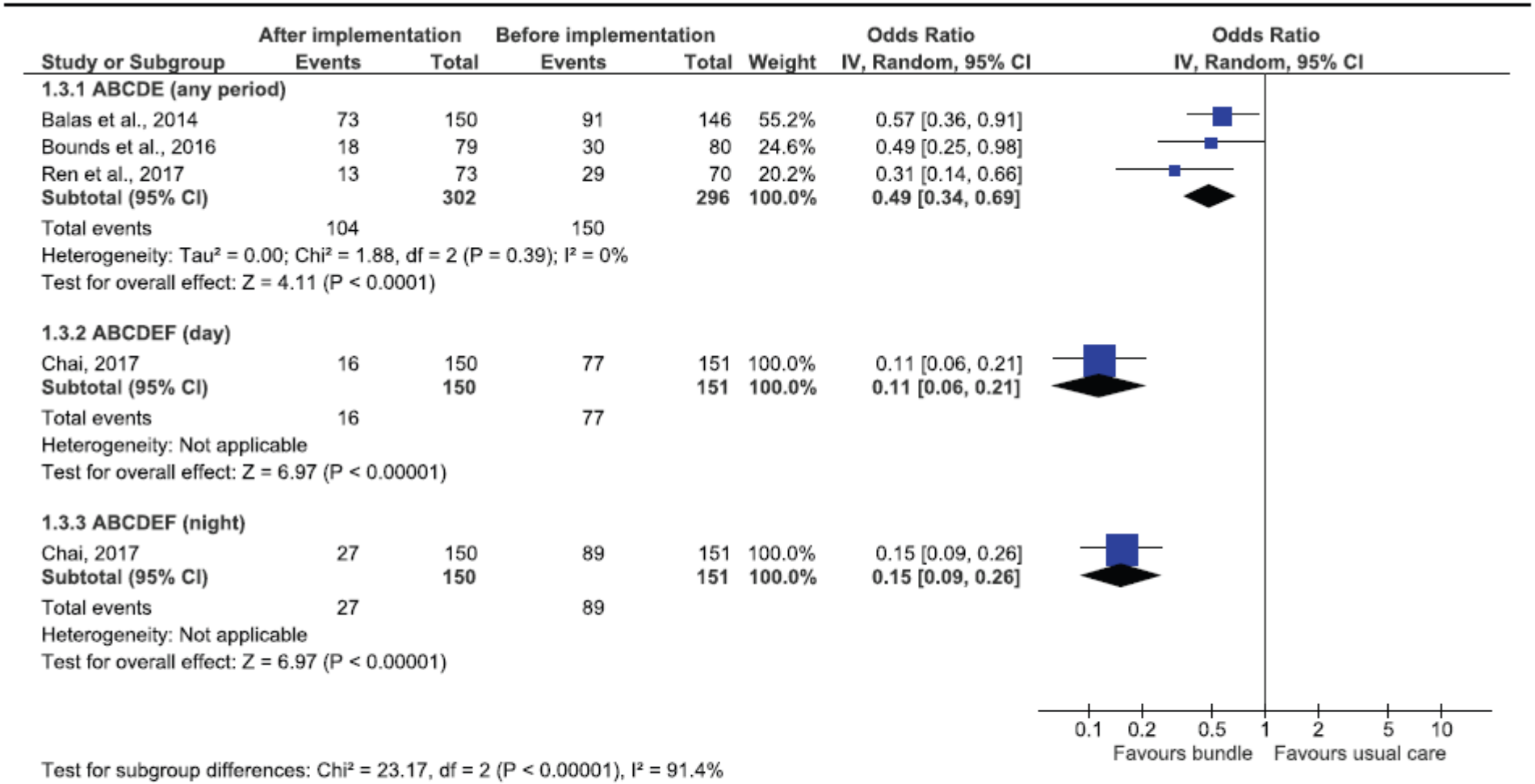


Figure 4. Forest plot summarizing the effects of ABCDE and ABCDEF bundles implementation for delirium outcome, assessed with Confusion Assessment Method in Intensive Care Unit (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC). ABCDE=Awakening and Breathing Coordination of daily sedation and ventilator removal trials, Delirium monitoring and management, and Early mobility and exercise; ABCDEF=Assessment, prevent and manage pain, Both spontaneous awakening and spontaneous breathing trials, Choice of analgesia and sedation, assess, prevent and manage Delirium, Early mobility and exercise, Family engagement.

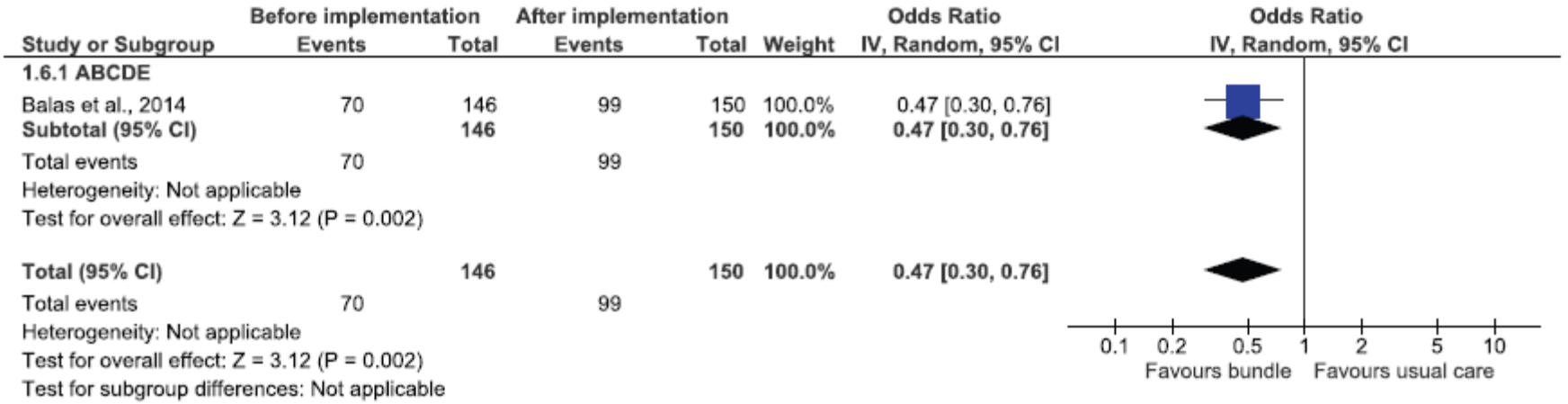


Figure 7. Forest plot summarizing the effects of ABCDE bundle implementation for early mobilization outcome, in percentage. ABCDE = Awakening and Breathing Coordination of daily sedation and ventilator removal trials, Delirium monitoring and management, and Early mobility and exercise.

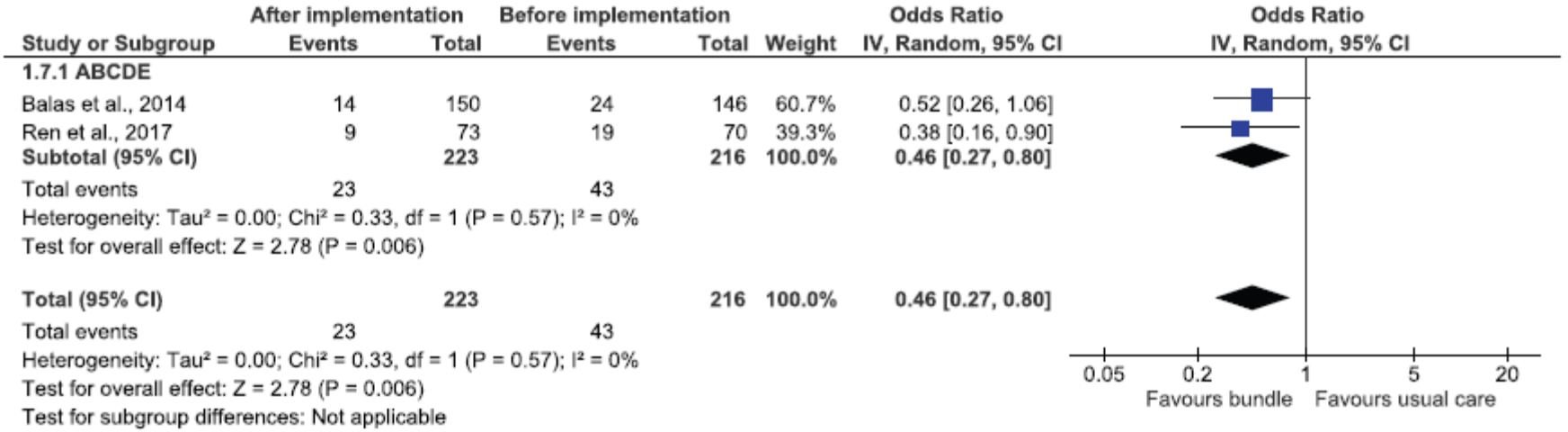


Figure 8. Forest plot summarizing the effects of ABCDE bundle implementation for ICU mortality outcome, in percentage. ABCDE = Awakening and Breathing Coordination of daily sedation and ventilator removal trials, Delirium monitoring and management, and Early mobility and exercise; ICU = intensive care unit.

Barriers and facilitators concerning perceptions and attitudes of health professionals in the implementation process.

Barriers	Facilitators
Communication challenges (n = 7)	Leaders' involvement (n = 7)
Lack of planning (n = 6)	Training (n = 6)
Excess documentation (n = 5)	Multidisciplinarity (n = 5)
Fear of risks to the patient (n = 5)	Practice-oriented training (n = 3)
Lack of formalization of the bundle (n = 3)	Carrying out planning (n = 3)
Lack of professional staff (n = 3)	Protocol consolidation (n = 3)
High workload (n = 3)	Strengthening organizational culture (n = 2)
Methodological problem (n = 2)	Performance evaluation (n = 2)
High staff turnover (n = 2)	Continuing education (n = 2)
Process resistance (n = 2)	Interdisciplinarity (n = 2)
Lack of motivation (n = 1)	Strengthening communication (n = 2)
	Checking records (n = 1)
	Audit (n = 1)
	Family involvement (n = 1)
	Dedicated team (n = 1)

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

Table 2. Primary and Secondary Outcomes.

Outcome	Nonsedation Group (N = 349)	Sedation Group (N = 351)	Difference (95% CI)*
Primary outcome			
All-cause mortality at 90 days after randomization — no. (%)	148 (42.4)	130 (37.0)	5.4 (−2.2 to 12.2)†
Secondary outcomes			
No. of days until death up to 90 days after randomization			
Median	13	12	1 (−2 to 5)
Interquartile range	6 to 27	5 to 28	
Patients with a major thromboembolic event at 90 days after randomization — no. (%)	1 (0.3)	10 (2.8)	−2.5 (−4.8 to −0.7)
No. of days free from coma or delirium within 28 days after randomization			
Median	27	26	1 (0 to 2)
Interquartile range	21 to 28	22 to 28	
Highest measured RIFLE score within 28 days after randomization‡			
Median	2	2	0 (−1 to 1)
Interquartile range	1 to 4	1 to 4	
No. of days in the ICU until death or 28 days after randomization, whichever occurred first			
Median	13	14	−1 (−7 to 4)
Interquartile range	0 to 23	0 to 23	
No. of days without mechanical ventilation within 28 days after randomization			
Median	20	19	1 (−3 to 3)
Interquartile range	0 to 26	0 to 25	

Olsen HT et al, Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. N Engl J Med. 2020 Mar 19;382(12):1103-1111

	Non-sed	sed	
Type of admission — no. (%)			
Medical	244 (69.9)	235 (67.0)	2.9 (–3.8 to 9.8)
Acute surgical	94 (26.9)	95 (27.1)	–0.2 (–6.5 to 6.5)
Elective surgical	11 (3.2)	21 (6.0)	–2.8 (–6.3 to 0.1)
Diagnosis at ICU admission — no. (%)			
Pneumonia or ARDS	147 (42.1)	151 (43.0)	–0.9 (–8.2 to 6.2)
Sepsis	84 (24.1)	74 (21.1)	3.0 (–3.2 to 9.2)
Exacerbation of COPD	24 (6.9)	21 (6.0)	0.9 (–2.7 to 4.8)
Gastrointestinal bleeding	4 (1.1)	4 (1.1)	0.0 (–1.8 to 1.8)
Trauma	11 (3.2)	18 (5.1)	–1.9 (–5.1 to 1.0)
Severe acute asthma	11 (3.2)	7 (2.0)	1.2 (–1.4 to 3.6)
Postoperative complications	7 (2.0)	7 (2.0)	0.0 (–2.3 to 2.3)
Other	66 (18.9)	74 (21.1)	–2.2 (–7.9 to 3.9)

What do we get?

- Light sedation with sedation interruption is as better as no sedation without any different in outcomes
- But the requirment of analgesic dose (morphine 0.0073 mcg/kg/hour vs 0.0060 mcg/kg/hour) is higher in non-sedation group. Also the non-sedation required intermittent boluses to provide patient comfort

Agents for pain control

- Opioids – fentanyl, remifentanil, alfentanil, sufentanil, morphine, methadone

- Non-opioids:
  - Acetaminophen
  - Nefopam
  - Ketamine
  - Neuropathic medications – gabapentin, carbamazepine, pregabalin

Others : Music, Massage

Remifentanil

Study	No. of studies	Comparator	Outcomes assessed	comments
Meta-analysis	15 studies	Other opioids (fentanyl, morphine, sufentanil)	Primary outcome: Duration of MV Secondary outcome: weaning time, ICU LOS, hospital LOS, side effects ,mortality, and costs.	Duration of MV reduced(P value=0.01) Decreased weaning time and reduced length of ICU stay (P value <0.05) No difference in mortality or side effect profile Cost is higher with remifentanil

Yang S et al,Comparison between remifentanil and other opioids in adult critically ill patients: A systematic review and meta-analysis. Medicine (Baltimore). 2021 Sep 24;100(38):e27275

Table 1

Main characteristics of the 17 studies included in the systemic review and meta-analysis.

				Intervention		Outcomes						
Study ID	Size	Patients	Setting	Remifentanil group	Control group	Intubation time	Weaning time	ICU LOS	Hospital LOS	Side effects	Mortality	Costs
Bhavsar 2016	60	Post-cardiac surgery	CICU	Remifentanil	Sufentanil	Yes	NR	Yes	NR	NR	NR	NR
Breen 2005	105	Other post-surgery	ICU	Remifentanil	Morphine or fentanyl	NR	NR	NR	NR	Yes	Yes	NR
Carrer 2007	100	Other post-surgery	ICU	Remifentanil	Morphine	Yes	NR	Yes	NR	Yes	NR	NR
Dahaba 2004	40	Other post-surgery	ICU	Remifentanil	Morphine	Yes	NR	Yes	NR	Yes	NR	NR
Engoren 2001a	62	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	NR	NR	Yes
Engoren 2001b	57	Post-cardiac surgery	ICU	Remifentanil	Sufentanil	yes	NR	Yes	yes	NR	NR	Yes
Guggenberger 2006	50	Post-cardiac surgery	SICU	Remifentanil	Sufentanil	Yes	NR	Yes	Yes	NR	NR	NR
Karabinis 2004a	69	Other post-surgery	ICU	Remifentanil	Fentanyl	Yes	Yes	NR	NR	NR	NR	NR
Karabinis 2004b	75	Other post-surgery	ICU	Remifentanil	Morphine	Yes	Yes	NR	NR	NR	NR	NR
Khanykin 2013	64	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	NR	NR	NR
Lee 2014	96	Medical critically ill patients	ICU	Remifentanil	Morphine	Yes	Yes	Yes	NR	NR	Yes	NR
Liu 2013	60	Other post-surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	NR	Yes	NR	Yes
Liu 2017	70	Medical critically ill patients	ICU	Remifentanil + midazolam	Fentanyl	Yes	Yes	Yes	NR	NR	Yes	NR
Maddali 2006	117	Post-cardiac surgery	PCSU	Remifentanil	Fentanyl	Yes	NR	Yes	NR	NR	NR	NR
Muellejans 2004	152	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	NR	Yes	Yes	NR	Yes	NR	NR
Muellejans 2006	72	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	Yes	Yes	NR	Yes	NR	NR
Spies 2011	60	Medical critically ill patient	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	YES	NR	NR

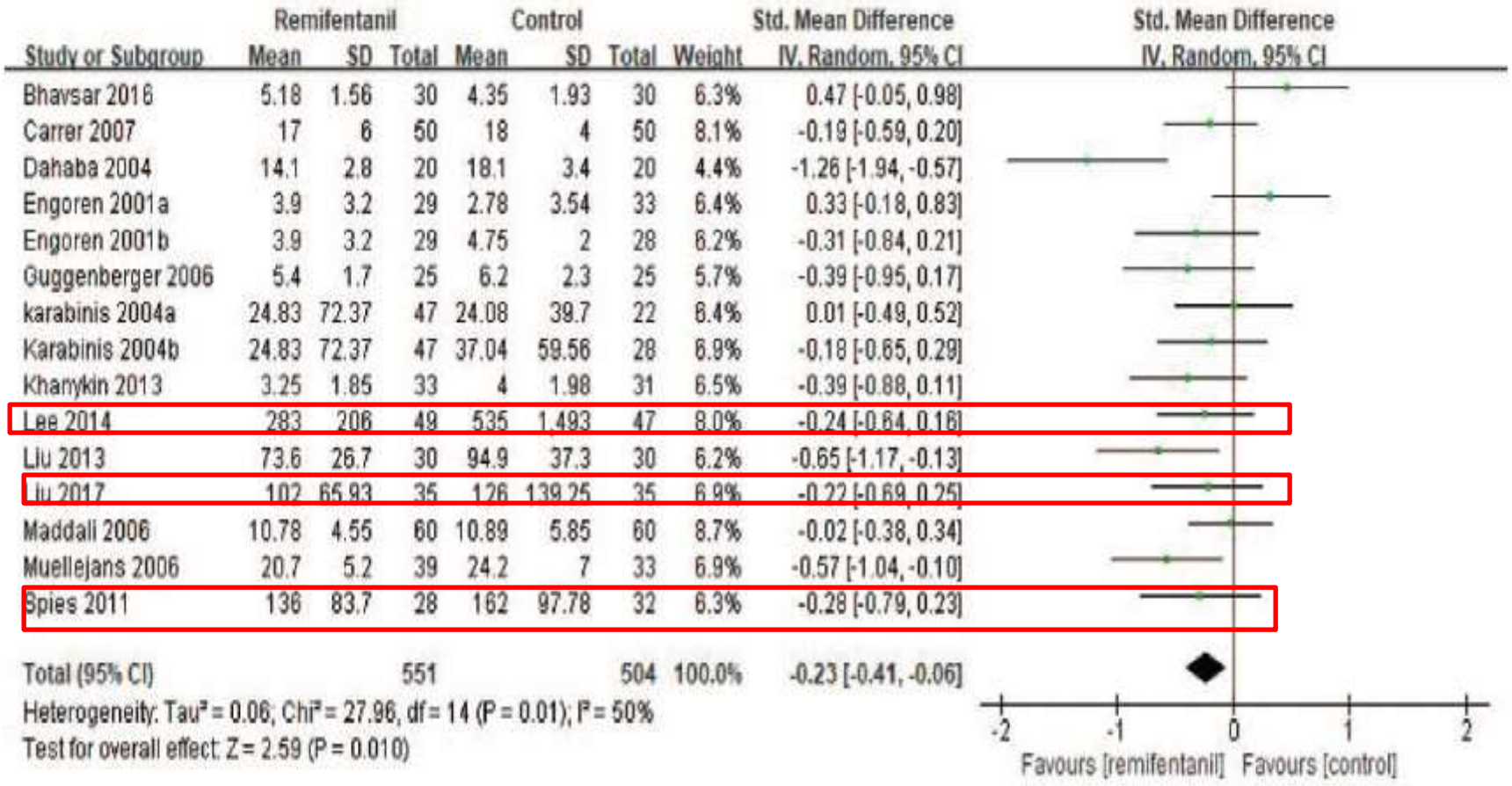


Figure 3. Forest plot comparing the duration of mechanical ventilation (h) between remifentanil and other opioids. CI: confidence interval; IV: inverse variance.

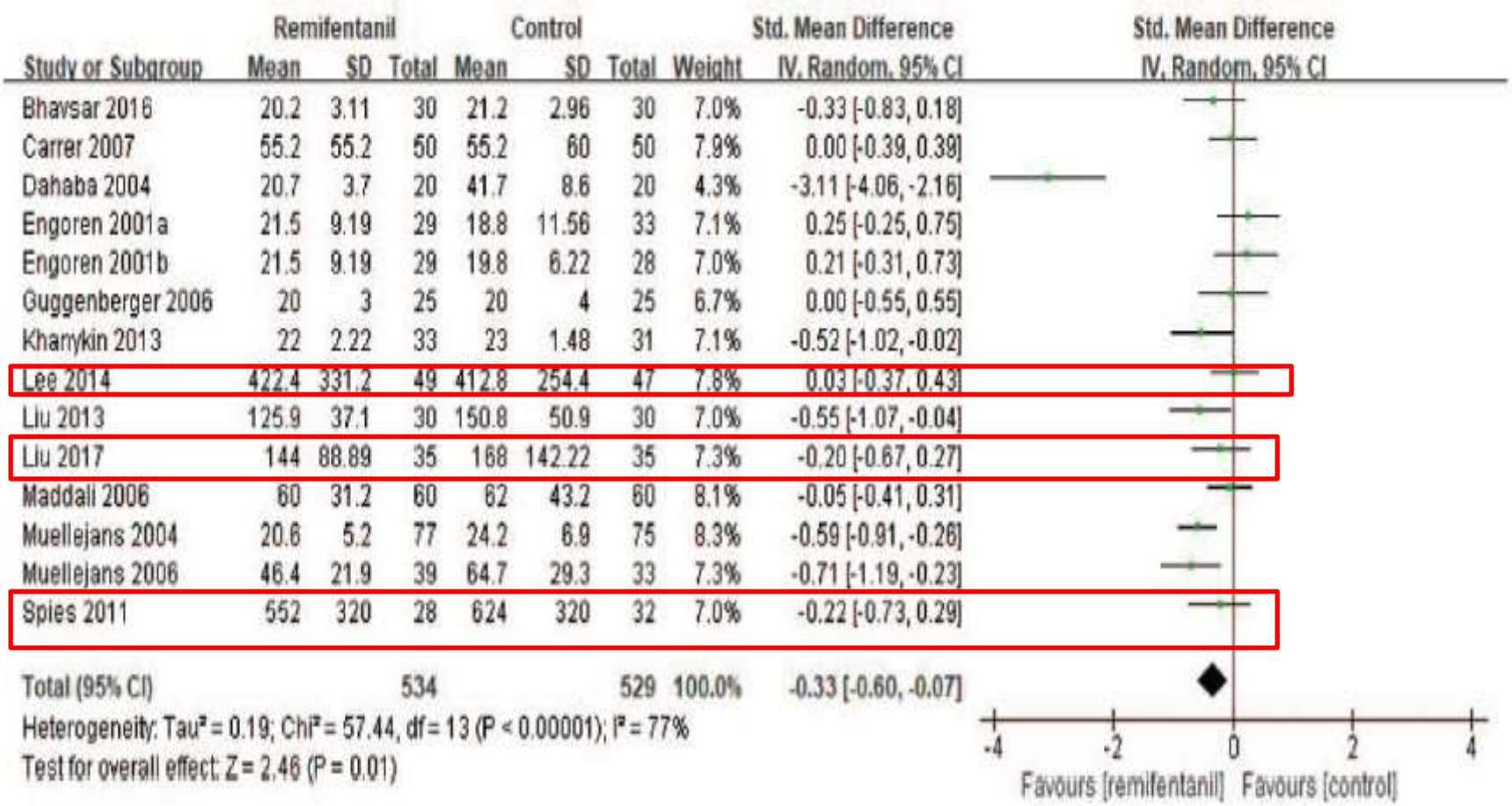


Figure 4. Forest plot comparing the ICU length of stay (h) between remifentanil and other opioids. CI = confidence interval; IV = inverse variance.

Study	No. of studies	Comparator	Outcomes assessed	comments
Meta-analysis	23 studies	Other opioids	Primary outcome: Duration of MV Secondary outcome: time to extubation after cessation of sedation,ICU LOS,hospital LOS,costs,mortality, agitation	Reduced duration of MV and time to extubation after cessation Other outcomes were not significant

Zhu Y, Wang Y, Du B, Xi X. Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis. Crit Care. 2017 Aug 3;21(1):206

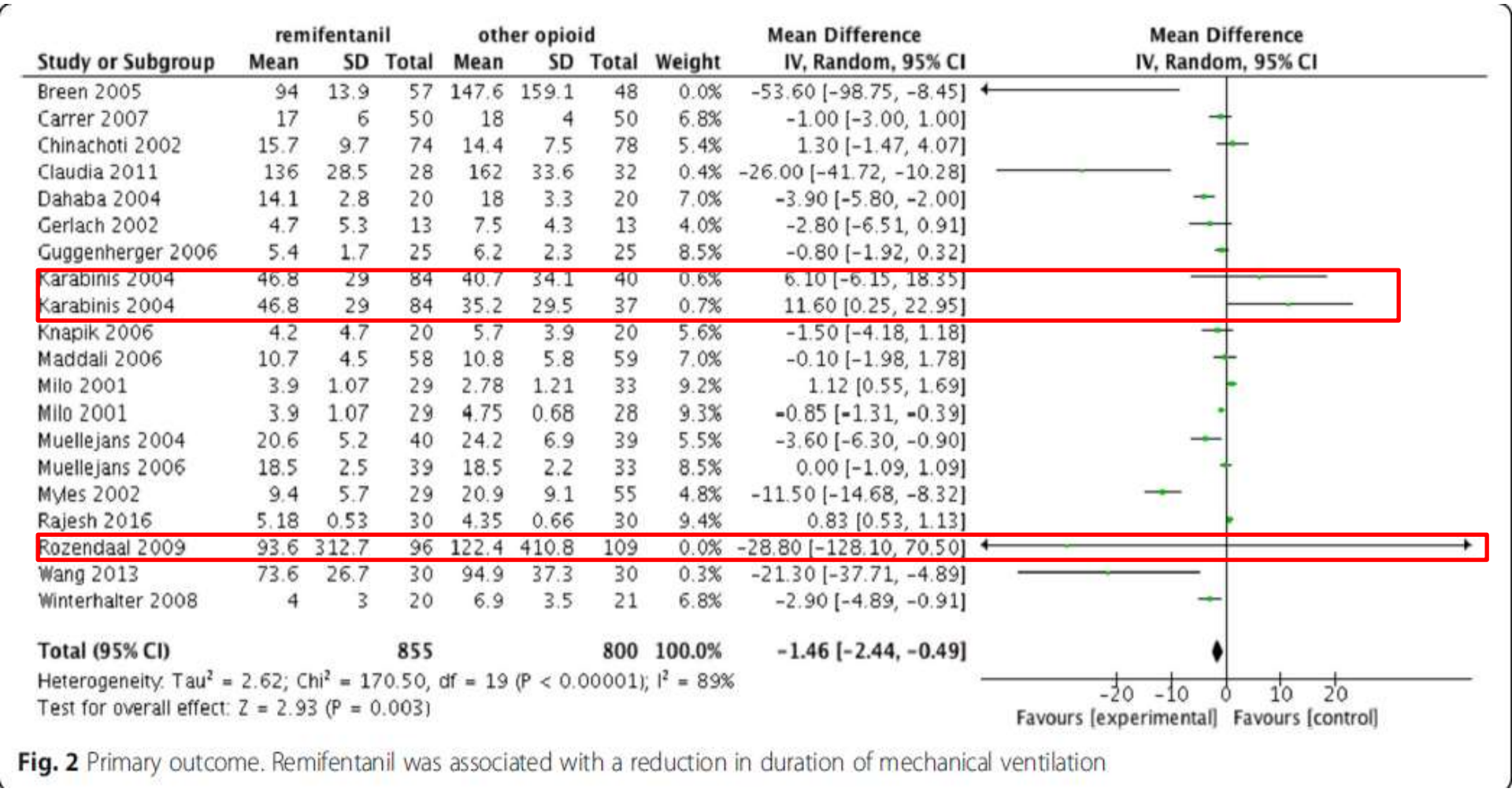


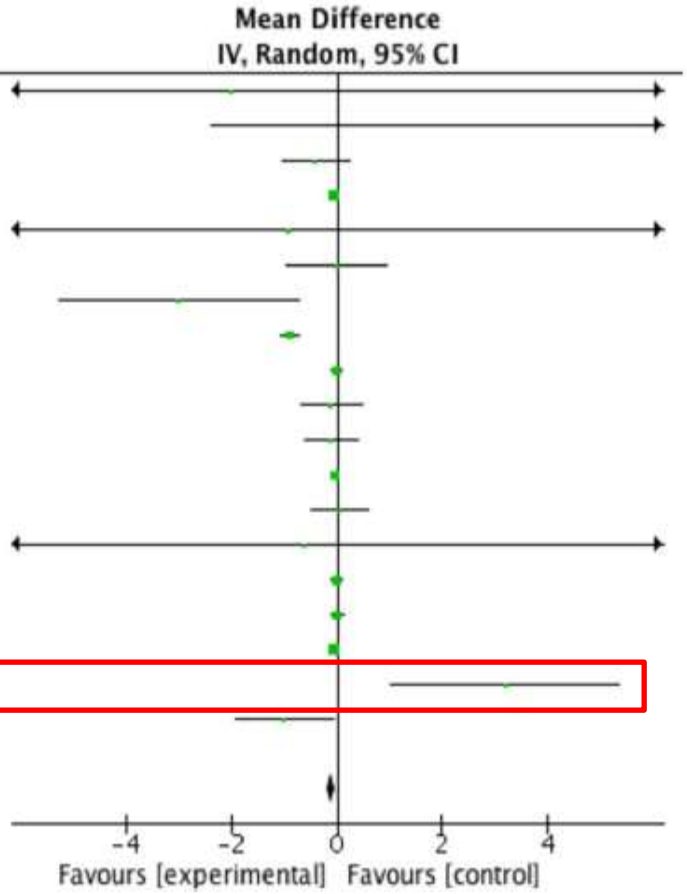
Fig. 2 Primary outcome. Remifentanil was associated with a reduction in duration of mechanical ventilation

b

Study or Subgroup	remifentanil Mean	SD	Total	other opioid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amor 2007	15	13	9	17	11	10	0.0%	-2.00 [-12.89, 8.89]
Baillard 2005	26	18.5	21	19	11.5	20	0.0%	7.00 [-2.38, 16.38]
Berdirli 2007	1.7	1.2	25	2.1	1.1	25	0.9%	-0.40 [-1.04, 0.24]
Boris 2013	0.91	0.03	33	0.95	0.02	31	17.7%	-0.04 [-0.05, -0.03]
Breen 2005	7.8	18.7	57	8.7	19.7	48	0.0%	-0.90 [-8.29, 6.49]
Carrer 2007	2.3	2.3	50	2.3	2.5	50	0.4%	0.00 [-0.94, 0.94]
Claudia 2011	23	4.5	28	26	4.5	32	0.1%	-3.00 [-5.28, -0.72]
Dahaba 2004	0.86	0.15	20	1.74	0.36	20	7.7%	-0.88 [-1.05, -0.71]
Guggenherger 2006	0.83	0.12	13	0.83	0.16	13	11.7%	0.00 [-0.11, 0.11]
Maddali 2006	2.5	1.3	58	2.6	1.8	59	1.2%	-0.10 [-0.67, 0.47]
Maddali 2006	2.5	1.3	58	2.6	1.5	59	1.4%	-0.10 [-0.61, 0.41]
Milo 2001	0.78	0.16	29	0.82	0.08	28	15.0%	-0.04 [-0.11, 0.03]
Muellejans 2004	1.7	1.68	77	1.65	1.69	74	1.3%	0.05 [-0.49, 0.59]
Muellejans 2006	2.1	0.9	40	2.7	28.9	39	0.0%	-0.60 [-9.67, 8.47]
Myles 2002	0.95	0.2	29	0.95	0.12	24	13.3%	0.00 [-0.09, 0.09]
Myles 2002	0.96	0.2	29	0.95	0.22	24	11.3%	0.01 [-0.10, 0.12]
Rajesh 2016	0.84	0.04	30	0.88	0.04	30	17.5%	-0.04 [-0.06, -0.02]
Rozendaal 2009	5.9	10.4	96	2.7	2.3	60	0.1%	3.20 [1.04, 5.36]
Wang 2013	5.2	1.5	30	6.2	2.1	30	0.5%	-1.00 [-1.92, -0.08]
Total (95% CI)			**732**			**676**	**100.0%**	**-0.10 [-0.16, -0.03]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 117.75$, df = 18 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: Z = 3.00 (P = 0.003)



Fentanyl

Study	No. of studies/subject	Comparator	Outcomes assessed	comments
Meta- analysis	7 studies	Fentanyl vs morphine, remifentanil	Primary outcome: mortality Secondary outcome: duration of mechanical ventilation, duration of the ICU stay, incidence of severe adverse events and incidence of delirium.	No mortality benefit No significant difference in duration of mechanical ventilation, length of ICU stay or incidence of delirium compared with other opioids
Cluster, cross over randomized control trial (ANALGESIC trial)	Fentanyl (344) and morphine (337)	Fentanyl versus morphine	Primary outcome: ventilator free days at day 28 Secondary outcome: Duration of ventilation, ICU free days and hospital free days at day 28, ICU mortality	None of the outcome were significant

Aoki Y et al, Effects of fentanyl administration in mechanically ventilated patients in the intensive care unit: a systematic review and meta-analysis. BMC Anesthesiol. 2022 Oct 21;22(1):323. Casamento AJ, Serpa Neto A, Young M, Lawrence M, Taplin C, Eastwood GM, Ghosh A, Bellomo R. A Phase II Cluster-Crossover Randomized Trial of Fentanyl versus Morphine for Analgosedation in Mechanically Ventilated Patients. Am J Respir Crit Care Med. 2021 Dec 1;204(11):1286-1294

Sedation agents

- Benzodiazepines – midazolam, lorazepam
- Propofol
- Dexmedetomidine
- Ketamine

Certain points before going into the agents

- Most of the agents we use in ICU are studied in the post cardiac surgery and elective post surgical patients

- Guidelines suggest same protocol to be applied to every patient. But considering the different patient profile in ICU, application of the same protocol to every patient could not be logical

- We should approach the studies from protocolised sedation and analgesia perspective to patient need's based and relevant ICU profile based sedation and analgesia approach

Shehabi, Y.,et al, Optimal Sedation and Pain Management: A Patient-and Symptom-Oriented Paradigm. *Seminars in Respiratory and Critical Care Medicine*, *42*(1), 98-111

- Common outcomes assessed in most of studies : Duration of mechanical ventilation, ICU length of stay, hospital length of stay, time to extubation, delirium incidence, mortality
- Long term neuro-cognitive outcome is scarce in the available literature (PTSD,depression) (PADIS guidelines 2018)
- ICU patient being intubated for prolonged period, ideally long term safety data of the agents (like thromboembolic events) are needed. Unfortunately the availability of such data in literature is scarce
- Multi-modal analgesia concept is less applicable in medical – critically ill patients

Devlin JW et al, Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018 Sep;46(9):e825-e873

- PADIS guidelines 2018 addresses mainly 3 agents benzodiazepines, propofol and dexmedetomidine

- It suggests clinically significant effect as shortened time to light sedation of atleast 4 hours and time to extubation of atleast 8-12 hours

Ketamine

- PADIS guidelines 2018 recommends ketamine as an non-opioid analgesic agent to be used in post surgical patients from available evidence
- Ketamine in ICU data showed that ketamine is able to reduce the dose of other sedatives and analgesic agents but that has not transformed into decreased incidence of delirium
- Cardiovascular safety profile of ketamine in ICU patients is lacking beyond 48 hours in literature
- Whether ketamine can be beneficial in specific population (like septic shock, ARDS) is also not available in the literature

Devlin JW et al, Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018 Sep;46(9):e825-e873

RESEARCH ARTICLE

Safety and feasibility of continuous ketamine infusion for analgosedation in medical and cardiac ICU patients who received mechanical ventilation support: A retrospective cohort study

Hohyung Jung[1☯], Jihye Lee[1☯], Hyun Young Ahn[2], Jeong Hoon Yang[1,3], Gee Young Suh[1,4], Ryoung-Eun Ko[1*], Chi Ryang Chung[1,5*]

Key population	**Total of 564 patients, cardiovascular disease (16%), respiratory disease (10.8%) 57.4% were admitted with respiratory failure, 19.5% with sepsis, 16.7% with CV illness, 69.5% on vasopressor support, RRT 15.8% >24 hours of mechanical ventilated Median length of ventilator support – 6.7 days (3.1 to 13.4)**
Intervention	CI ketamine (atleast 8 hours, maximum 67 hours , median 33.3 hours) with concomitant sedatives
Comparator	Before and after ketamine infusion (8-0 hours, 0-8 hours,8-16 hours, 16-24 hours)
Outcome	Vasopressor inotropic score (hemodynamic stability), delirium
Results	Vasopressor inotropic score no increase, delirium prevalence static before and after infusion Long term cardiovascular safety is limited in this study Sub-group analysis is not available

Jung H et al, Safety and feasibility of continuous ketamine infusion for analgosedation in medical and cardiac ICU patients who received mechanical ventilation support: A retrospective cohort study. PLoS ONE 17(9): e0274865

OBSERVATIONAL STUDY

OPEN

Multicenter Retrospective Review of Ketamine Use in the ICU

Key population	Multicenter (25) ICU, 390 patients, medical (35.3%), 80% on MV, RF – 22%, Vasopressor 33.9%, NMBA – 9.2%
Intervention	CI ketamine (0.1 to 0.5 mg/kg/hr) median-1.6 days (0.9 to 2.9 days)
Comparator	Before and after ketamine infusion
Outcomes	Pain/sedation scores Cumulative use of sedatives and analgesics Delirium (1st 7 days/until sedation whichever earlier)
Results	Although ketamine able to reduce the dose of sedatives, it does not transform into decreased incidence of delirium Hemodynamic parameters were stable but are available for 48 hours only (sub-group data not available)

Groth CM et al,. Multicenter Retrospective Review of Ketamine Use in the ICU. Crit Care Explor. 2022 Feb 10;4(2):e0633

Propofol – question to answer

- Any mortality benefit?
- Any advantage over other agents?
- Safety profile of the agent in ICU?

Propofol

Study	Population	Intervn.	Compar.	Outcome	Results
Meta-analysis (252 studies)	ICU patients (mostly non-cardiac surgery)	IV propofol	Other sedatives	Mortality	Mortality was higher with propofol group (5.2% vs 4.3%)
observational cohort study	MV patients with >60mcg/kg/min for >24 hours	IV propofol	-	Incidence of PRIS mortality	Incidence of PRIS was 2.9% Mortality was 36.8%
RCT	ARDS on MV with >12 hrs NMBA infusion	propofol	Midaz	RASS -2 after discontinuation of NMBA	Propofol is better to return to RASS -2 when NMBA is discontinued

Kotani, Y et al, Propofol and survival: an updated meta-analysis of randomized clinical trials. *Crit Care* **27**, 139 (2023)
Li WK et al, The incidence of propofol infusion syndrome in critically-ill patients. J Crit Care. 2022 Oct;71:154098
Addison JD,et al, A Comparison of Midazolam and Propofol for Deep Sedation in Patients with Acute Respiratory Distress Syndrome Requiring Neuromuscular Blocking Agents. J Pharm Pract. 2022 Oct 2:8971900221131420

Dexmedetomidine

- Data from SEDCOM trial suggest that when compared with BZD, dexmedetomidine facilitated extubation 1.9 days earlier and decreased the incidence of delirium
- Other pooled studies from PADIS 2018 guidelines suggest that when compared with benzodiazepines, dexmedetomidine does not affect the length of ICU stay, extubation time, duration of mechanical ventilation and risk of delirium

Study	Population	Intervn.	Compar.	Outcome	Results
Meta-analysis (19 studies)	Sepsis with/wout MV	IV dexamed	Other sedatives (Propofol OR BZD)	Mortality	Mortality benefit only when compared with BZD
Sub-group analysis of SPICE III trial (83 patients)	Septic shock on inotropes	Early sedation with dexmed	Usual care (propofol, midaz, others)	Vasopressor requirement at 48 hours	Requirement did not increase at 48 hours. So can be used in septic shock patients
MENDS trial	Sepsis on MV	Dexmed	Propofol	TICS-T	25% in each group has cognitive impairment at the end of 6 month (39 vs 38)
RCT	Septic shock on MV	Dexmed	Propofol	AKI incide.(data collected upto 5D)	38% vs 60% W.R.T dexmed and propofol

Zhang T et al,Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials. Ann Intensive Care. 2022 Aug 27;12(1):81.
Hughes CG et al, Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med. 2021 Apr 15;384(15):1424-1436.
Cioccari L et al, The effect of dexmedetomidine on vasopressor requirements in patients with septic shock: a subgroup analysis of the Sedation Practice in Intensive Care Evaluation [SPICE III] Trial. Crit Care. 2020 Jul 16;24(1):441

- At present in our ICU we use midazolam for sedation, compared to which most of the studies suggests a mortality benefit with dexmedetomidine
- Also dexmedetomidine has been shown, that it does not worsen hemodynamic parameters or inotropic requirement which is again a favouring factor to use in our ICU

Multi-modal analgesia concept

- Use of agents with different mechanism of action to control pain
- Opioid is the drug of choice in non-neuropathic pain in critically ill patients
- Combining other analgesics reduces the requirement of the opioid agents thereby minimizing the adverse effects
- Protocol based administration of analgesic and sedative agents are necessary to avoid overuse of these agents

Impact of a Multimodal Analgesia Protocol in an Intensive Care Unit: A Pre-post Cohort Study

Renato Lucas P. de Souza Sr. [1], João Abrão [1], Luís V. Garcia [1], Sofia Vila Moutinho [2], Ester Wiggers [3], Andiamira Cagnoni Balestra [4]

- A single center ICU based pre and post cohort study
- 468 subjects (pre-intervention) and 1508 subjects (post intervention) included
- Multi-modal analgesia protocol was applied
- It was found that the fentanyl use was decreased by 20% after the implementation of multi-modal analgesia protocol

de Souza RLP Sr et al, Impact of a Multimodal Analgesia Protocol in an Intensive Care Unit: A Pre-post Cohort Study. Cureus. 2022 Mar 3;14(3):e22786

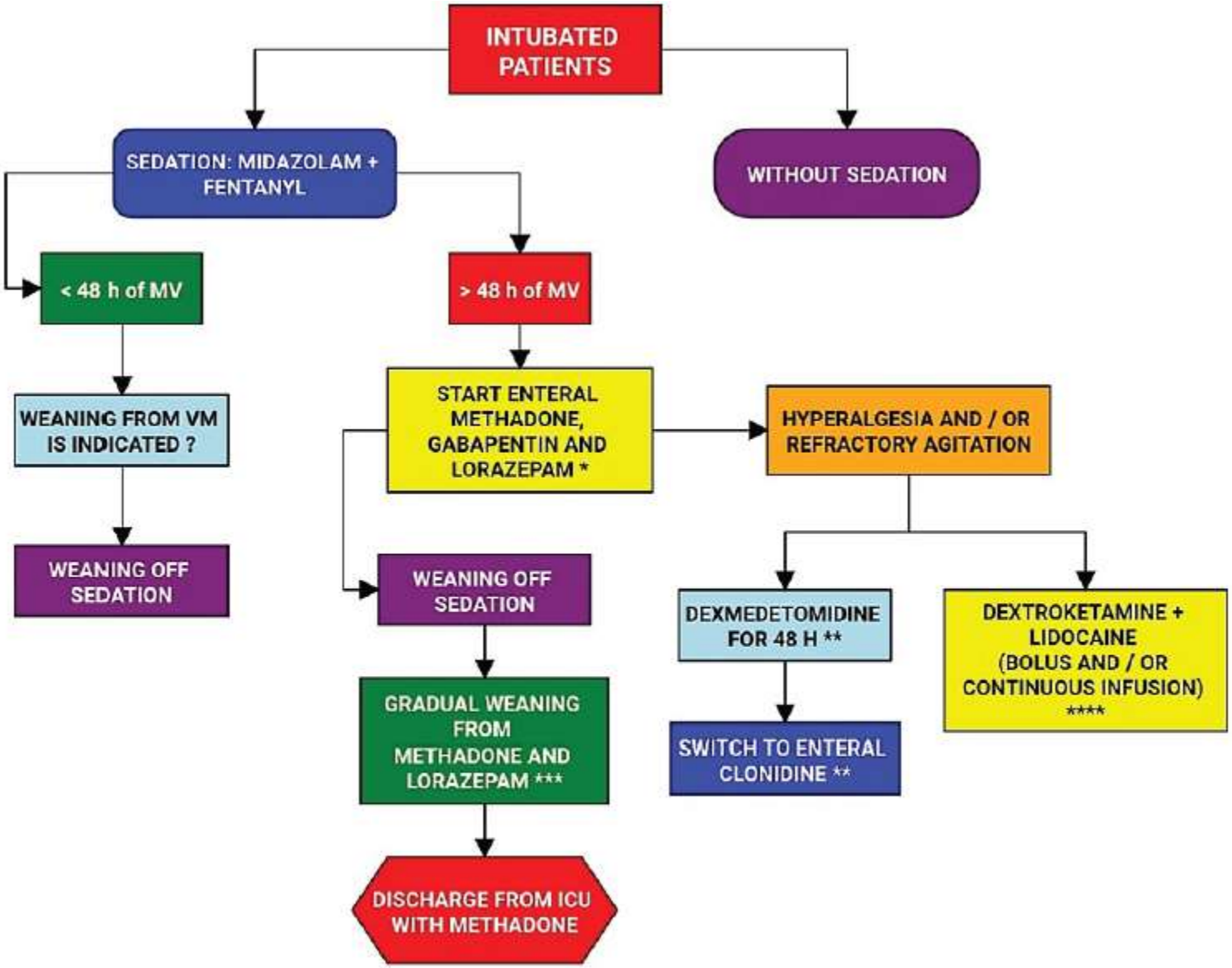


FIGURE 3: Multimodal analgesia flowchart in intubated patients

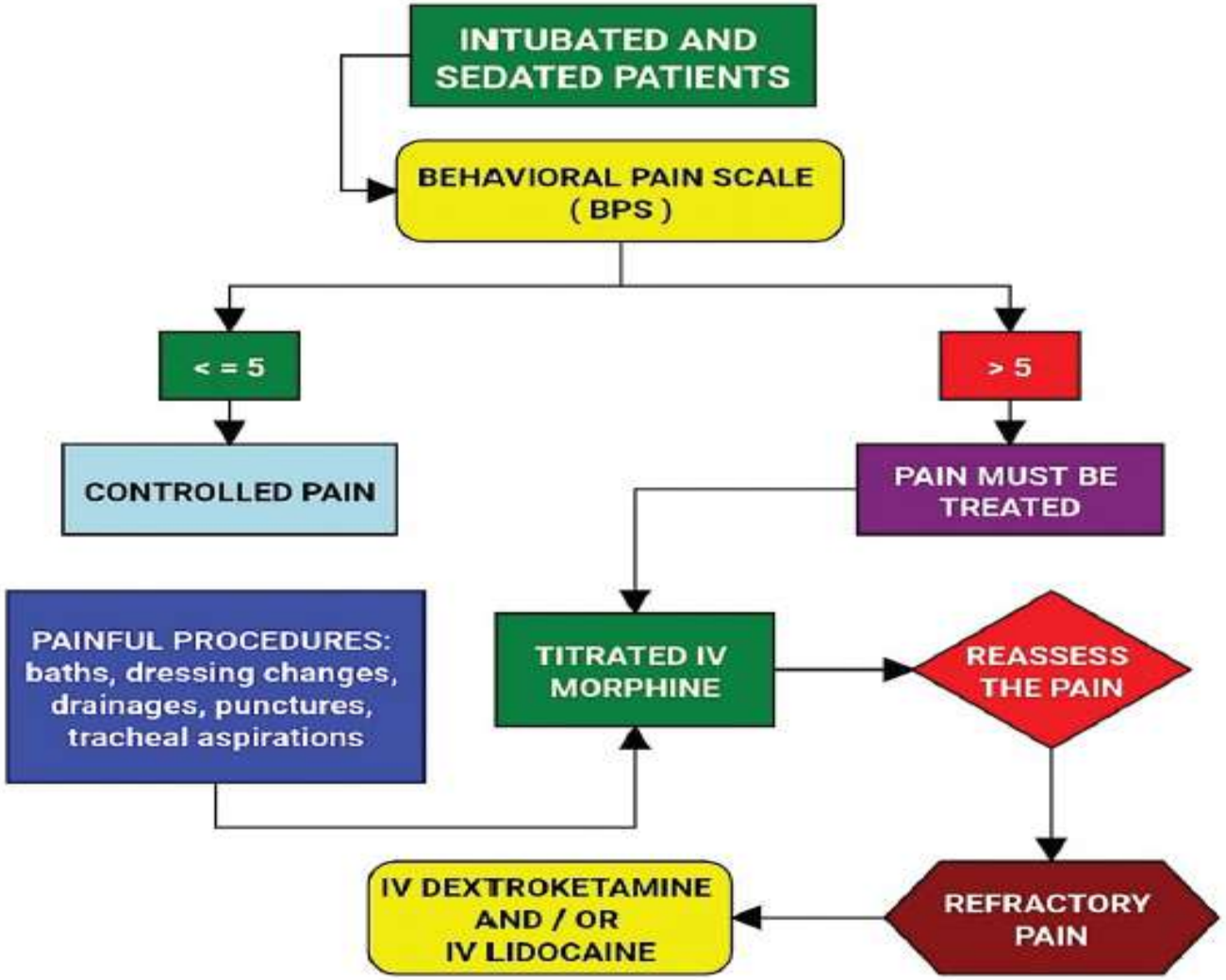


FIGURE 2: Flowchart of acute pain treatment in intubated and sedated patients

Analgo-sedation/analgesia first strategy/analgesia based sedation

- Analogsedation is defined as either analgesia-first sedation (i.e., an analgesic, usually an opioid, used before a sedative to reach the sedative goal) or analgesia-based sedation (i.e., an analgesic, usually an opioid, used instead of a sedative to reach the sedative goal)
- Has shown to reduce the duration of sedation effects thereby reduced ventilator time and ICU stay
- However there is no effect on mortality demonstrated in studies

Wang CT et al, The impact of analgosedation on mortality and delirium in critically ill patients: A systematic review and meta-analysis. Intensive Crit Care Nurs. 2019 Oct;54:7-14

Questions to answer

- What role does analgo-sedation have in medical critically ill patients?
- How to practice analgo-sedation in ICU?
- What advantage does analgo-sedation offer in ICU?

Review article

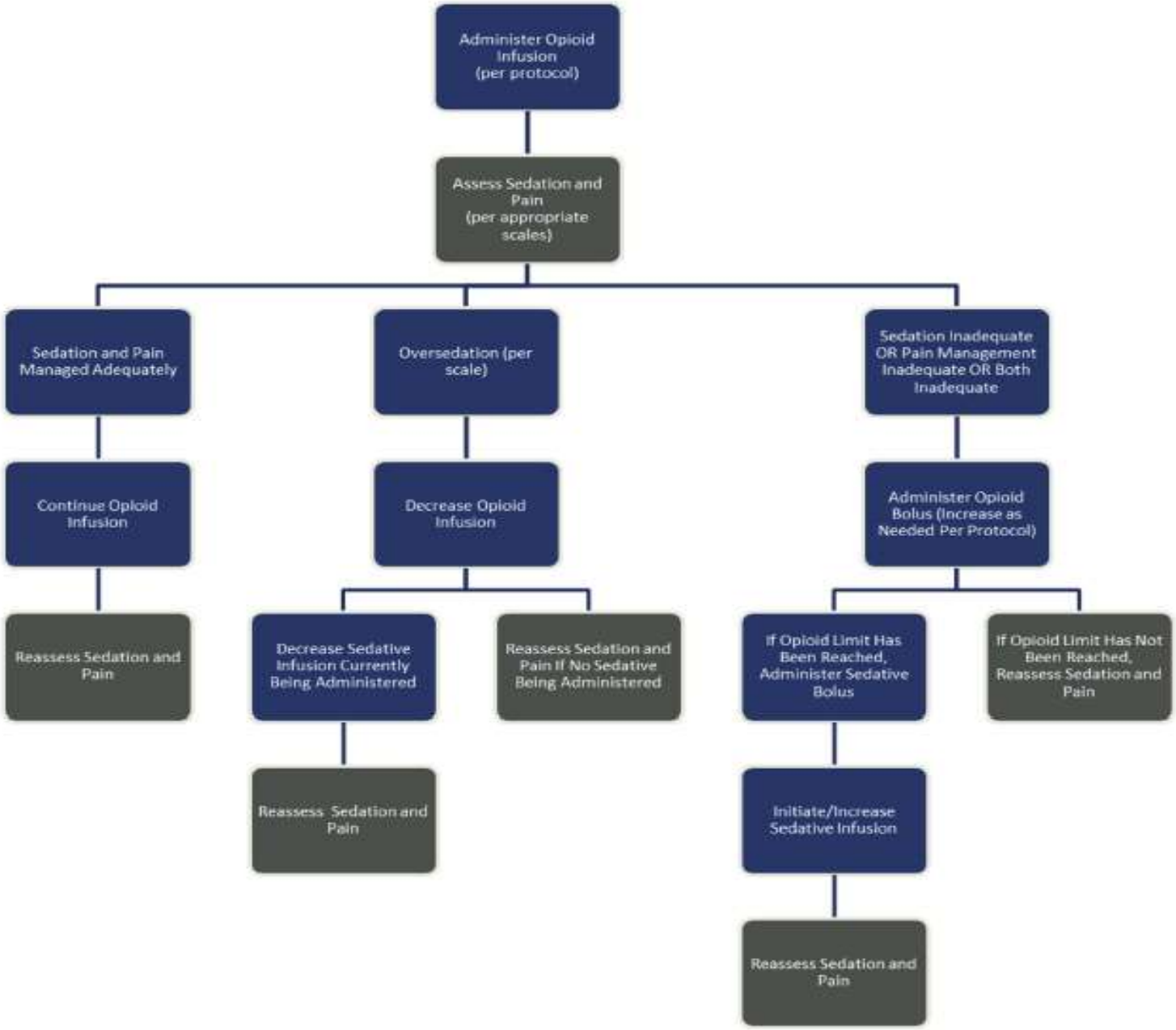
The impact of analgosedation on mortality and delirium in critically ill patients: A systematic review and meta-analysis ☆

Cui-Ting Wang [a,*], Yong Mao [b], Ling Zhao [a], Bin Ma [c]

[a] The People's Hospital of Zhuhai, Zhuhai, Guangdong, China
[b] The Second Hospital of Lanzhou University, Lanzhou, Gansu, China
[c] Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Gansu, China

- The meta-analysis of 17 studies providing an insight whether analgo-sedation yield mortality benefit and improvement of delirium in ICU
- The studies includes RCTS, case control studies and cohort studies
- Main comparator was hypnotic based regimen versus analgosedation
- Analgosedation seems to overall improved the ICU mortality rate (odds ratio – 0.72, P - 0.03). But when sub-group analysis were performed there was no mortality benefit in ICU as well as hospital mortality
- There was also no significant decrease in delirium, in fact there was increase in incidence of delirum (OR – 1.06, 0.78 to 1.4, P - value – 0.7)

Wang CT et al, The impact of analgosedation on mortality and delirium in critically ill patients: A systematic review and meta-analysis. Intensive Crit Care Nurs. 2019 Oct;54:7-14



Wiatrowski R et al, Analgosedation: Improving Patient Outcomes in ICU Sedation and Pain Management. Pain Manag Nurs. 2016 Jun;17(3):204-17

Monitoring sedation

Clinical assessment

- Richmond agitation sedation scale(RASS)
- Sedation Agitation Scale (SAS)
- Ramsay sedation scale (RSS)

Objective monitoring

- Bispectral index(BI)
- Auditory evoked potential
- Narcotrend index (NI)
- Patient state index(PSI)
- State Entropy (SE)

Bispectral index monitoring

- Continuous EEG monitoring of cerebral activity
- Has numerical scoring from 0 to 100
- Target is to keep between 50 to 60
- Proven role in patients who are anaesthetized
- Evidence regarding role of bispectral monitoring compared to clinical assessment scales (RASS, SAS) in ICU patients does not have influence on length of mechanical ventilation, ICU length of stay and adverse effects

Weatherburn C et al, The impact of bispectral index monitoring on sedation administration in mechanically ventilated patients. Anaesth Intensive Care. 2007 Apr;35(2):204-8
Shetty RM et al, BIS monitoring versus clinical assessment for sedation in mechanically ventilated adults in the intensive care unit and its impact on clinical outcomes and resource utilization. Cochrane Database Syst Rev. 2018 Feb 21;2(2):CD011240

Richmond sedation agitation scale

- Clinical assessment scale to assess the depth of sedation in ICU patients
- Goal is to maintain sedation at a level of -2 to -3

RASS score

Richmond Agitation & Sedation Scale				CAM-ICU
Score	**Description**			
+4	Combative	Violent, immediate danger to staff		RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive		
+2	Agitated	Frequent non-purposeful movements, fights ventilator		
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous		
0	Alert & calm			
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice	
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)		
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)		RASS < -2 STOP Recheck later
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Touch	
-5	Un-rousable	No response to voice or physical stimulation		

Questions to answer

- Is BIS could be correlated with clinical assessment scales?
- If so, could it be used as alternative to clinical assessment scales?
- If BIS is an alternative, which ICU population could benefit from BIS use?
- Does BIS usage has other benefit also?
- What is the cost of using BIS in ICU?

Systematic review and meta-analysis of the correlation between bispectral index (BIS) and clinical sedation scales: Toward defining the role of BIS in critically ill patients

Mojdeh S. Heavner[1] | Emily F. Gorman[2] | Dustin D. Linn[3] | Siu Yan Amy Yeung[4]
Todd A. Miano[5]

- A meta-analysis of 24 studies which assessed the correlation between BIS and different clinical sedation scales (RASS, RSS, SAS)
- Important inclusion criteria in this meta-analysis was all patients were mechanically ventilated and both BIS & clinical assessment should almost happen at same time (<5 min)
- Although the studies included were heterogeneous (I^2 > 70%) there was better correlation of BIS with RASS 0.68 (0.61 -0.74), RSS 0.76 (0.69-0.82) and SAS 0.53 (0.42 – 0.63) at 95% CI (these were assessed before initiation of NMBA)
- This meta-analysis revealed that there is often a ceiling effect between the sedation scales and BIS at higher level of arousal and flooring effect at lower level of arousal

Heavner MS et al, Systematic review and meta-analysis of the correlation between bispectral index (BIS) and clinical sedation scales: Toward defining the role of BIS in critically ill patients. Pharmacotherapy. 2022 Aug;42(8):667-676

- So, the BIS monitoring have better role in monitoring deeply sedated patients where clinical sedation scales have their limitation
- At higher level of arousal, better are clinical assessment scales where BIS have its limitation
- The ideal candidates in our ICU are severe ARDS patients and in patients where NMBA are used
- BIS monitoring has its limitation of use in brain injury patients

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane Database of Systematic Reviews

[Intervention Review]

BIS monitoring versus clinical assessment for sedation in mechanically ventilated adults in the intensive care unit and its impact on clinical outcomes and resource utilization

- Meta- analysis of 4 studies
- Assessed bispectral monitoring versus clinical assessment on ICU length of stay (LOS), duration of mechanical ventilation, any cause mortality, risk of ventilator-associated pneumonia (VAP), risk of adverse events, hospital LOS, amount of sedative agents used, cost
- Overall, there was no difference in outcomes but objective monitoring incurs more cost

Shetty RM et al, BIS monitoring versus clinical assessment for sedation in mechanically ventilated adults in the intensive care unit and its impact on clinical outcomes and resource utilization. Cochrane Database Syst Rev. 2018 Feb 21;2(2):CD011240

Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Clinical assessment	Risk with BIS monitoring				
Intensive care unit length of stay (ICU LOS) (measured in days)	Median ICU LOS was 8 Days	Median ICU LOS was 4 Days higher	Mdn D 4 [Range 4 to 18]	50 (1 RCT)	⊕⊕⊖⊖ LOW [1]	
Duration of mechanical ventilation (measured in days)	Mean duration of mechanical ventilation was 2.49 days	Mean duration of mechanical ventilation was 0.02 days lower	MD -0.02 (-0.13, 0.09)	155 (2 RCTs)	⊕⊕⊖⊖ LOW [2]	
Adverse events: Measured as number of patients with adverse events				105 (1 RCT)	⊕⊖⊖⊖ VERY LOW [3]	Clinically relevant adverse events such as self-extubation or unplanned disconnection of indwelling catheters were not reported in any study.
	809 patients with restlessness after suction per 1000 patients	16 less patients with restlessness after suction	RR 1.11 (0.90,1.37)			
	714 patients with endotracheal tube resistance per 1000 patients	32 more patients with endotracheal tube resistance	RR 0.96 (0.75, 1.22)			
	928 patients with pain tolerance during sedation per 1000 patients	8 more patients with pain tolerance during sedation	RR 0.99 (0.89, 1.10)			
	47 patients with delirium after extubation per 1000 patients	32 less patients with delirium after extubation	RR 3 (0.28, 32.04)			

Thank you