Journal club

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Abbreviations

- ICU: intensive care unit
- CAM-ICU: Confusion Assessment Method for the ICU
- CPOT : Critical Care Pain Observation Tool
- RASS: Richmond Agitation-Sedation Scale
- NMB: neuromuscular blockade
- SAT: spontaneous awakening test
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Outline

- Background
- PICO
- Critical appraisal
- CASP系統性文獻回顧檢核表

Background

PAD guidelines

圖1、止痛鎮靜藥品使用評估流程: "Pain Control First"為原則

*詳細調整流程請見表1-1&附錄一

Pain (CPOT, table 2)	CPOT goal 0 ~ 2 每日重新審視 CPOT goal 至少Q2H評估	✧ CPOT 0-2: 維持現有止痛藥物劑量或調降止痛藥物劑量 ✧ CPOT >2: 排除可能病因，開始給予止痛藥物或調升止痛藥物劑量 ✧ 一旦改變藥物劑量→給藥後30分鐘後再次評估 ✧ 止痛藥物見表1
Agitation (RASS, table 3)	RASS goal -2 ~ 0 每日重新審視RASS goal 未使用鎮靜藥物: 每班至少評估1次 使用鎮靜藥物: 至少Q2H評估	✧ RASS < -2: 調降鎮靜藥物劑量 ✧ RASS -2~0: 維持現有鎮靜藥物劑量或調降鎮靜藥物劑量 ✧ RASS>0: 開始或調升鎮靜藥物劑量 ✧ 一旦改變藥物劑量→給藥後30分鐘後再次評估 ✧ 鎮靜藥物見表1
If RASS ≧-3		
Delirium (CAM-ICU, table 4) *CAM-ICU不適用於RASS -5~-4*	CAM-ICU goal (-) 每班至少評估一次 可視狀況prn加強評估 執行ABCDEF bundle	✧ 若CAM-ICU (+)，開始鑑別診斷找出可能原因並加強ABCDEF bundle (附錄二~七) ✧ 若為hyperactive delirium，可考慮加上譫妄藥物 ✧ 譫妄藥物見表1

P- Pain

- Routine pain assessment
- **Pain should be treated before a sedative agent is considered**
- **Opioids** : mainstay for pain management ICU settings
  - side effects : sedation, delirium, respiratory depression, ileus, and immunosuppression

Adjuvant therapy	
Acetaminophen	1g Q6H IV/PO: ↓pain intensity, opioid consumption
	(conditional, very low quality of evidence)
Ketamine	1–2 μg/kg/hr: ↓pain intensity, **post surgical patients**
	(conditional, very low quality of evidence)
Neuropathic pain medication	**gabapentin, carbamazepine, and pregabalin**
	Neuropathic pain (strong , moderate quality of evidence).
	Post cardiovascular surgery (conditional, very low quality of evidence)

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P- Pain

分類	學名/商品名/單位劑量	建議劑量	注意事項
止痛藥品	Morphine	2-5 mg Q4-6H PRN 連續輸注：2–30 mg/hr (稀釋液：NS 或D5W)	1. 肝腎功能不佳病人易造成劑量蓄積。 2. 可能引發低血壓、支氣管收縮、皮疹、熱潮紅等反應。 3. 生命跡象不穩定病人不建議使用。
	Fentanyl	12.5-25 mcg Q4-6H PRN 連續輸注：Start at 12.5 mcg/hr, range 0-150 mcg/hr (稀釋液：NS 或 D5W)	1. 適用於血液動力學相對不穩定之病人，較morphine不易造成低血壓風險，給藥後仍需密切監測。 2. 劑量較高時，可能造成胸壁僵直(chest wall rigidity)。 3. 肝腎功能不全需小心使用。

A- Agitation/Sedation

- **Suggest light sedation** (vs deep sedation) in critically ill, mechanically ventilated adults

  (conditional recommendation, low quality of evidence)

  - ↓time to extubation, ICU length of stay, tracheostomy rate
- **Suggest either propofol or dexmedetomidine over benzodiazepines** for sedation in critically ill, mechanically ventilated adults

  (conditional recommendation, low quality of evidence)

  - Improved **short-term outcomes** :
    - ICU length of stay , duration of mechanical ventilation, delirium
  - Dexmedetomidine v.s. propofol (PRODEX study)
    - **↓delirium incidence with dexmedetomidine (48 hours after sedation cessation)**
    - No differences in bradycardia or hypotension

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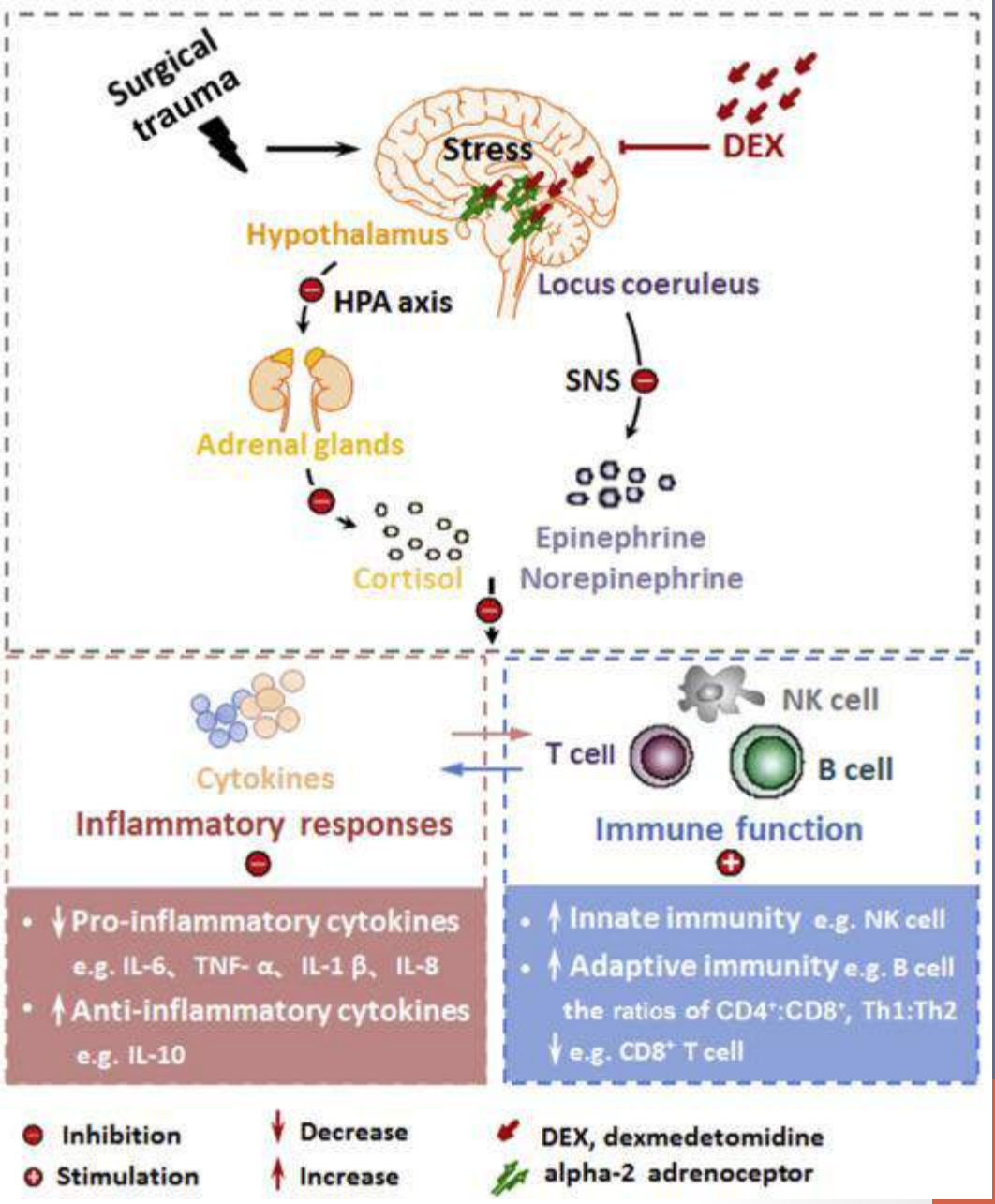
A-Agitation /Sedation

- Dexmedetomidine
  - anti-inflammatory effect ?



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A- Agitation/Sedation

鎮靜藥品	Midazolam	0.01-0.05 mg/kg PRN 連續輸注：Start at 0.02 mg/kg/hr, range 0-0.1 mg/kg/hr (稀釋液：NS 或 D5W)	1. 肝腎功能不佳病人易造成劑量蓄積。 2. 經肝代謝，肝功能不全需小心使用。 3. 體液不足的病人易發生低血壓。
	Lorazepam	0.02-0.06 mg/kg Q2-6H PRN 連續輸注：Start at 1 mg/hr, range 0-8 mg/hr (稀釋液：NS 或 D5W)	1. 可能引發低血壓、呼吸抑制。 2. 若連續輸注超過48小時，易造成 propylene glycol 堆積，引發腎衰竭。
	Propofol	5 mcg/kg/min over 5 min 連續輸注：Range 0-50 mcg/kg/min (稀釋液：可不用稀釋或D5W)	1. 流速或劑量超過 4 mg/kg/hr易發生 Propofol 輸注症候群 (代謝性酸中毒、心搏徐緩、橫紋肌溶解症、急性腎衰竭)，建議使用不超過 72 小時。 2. 建議每12小時更換propofol 輸注系統，以免細菌滋生。 3. 有hyperlipidemia 風險的病人建議監測 triglyceride
	Dexmedetomidine	連續輸注：Start at 0.2 mcg/kg/hr, range 0-1.5 mcg/kg/hr (稀釋液：NS)	1. 密切監測低血壓、心搏過慢。 2. 增加輸注速率間應至少間隔30分鐘。

D-Delirium

- We suggest **not routinely using haloperidol, an atypical antipsychotic** to treat delirium

  (conditional recommendation, low quality of evidence).

  - quetiapine , ziprasidone , olanzapine
- We suggest using **dexmedetomidine** for delirium in mechanically ventilated adults where agitation is **precluding weaning/extubation**

  (conditional recommendation, low quality of evidence)

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D-Delirium

分類	學名/商品名/單位劑量	建議劑量	注意事項
譫妄	Quetiapine	起始劑量: 25 mg BID PO; 在老人以及具 QTc prolongation 危險因子者，建議由較低劑量開始 (12.5 mg BID PO) 增加劑量: 可視需求每天增加 50 mg twice daily 最大劑量: 200 mg BID PO	1. 譫妄處置的優先選擇藥物 2. 相對較少 extrapyramidal symptoms (EPS)及QTc prolongation 3. 相對較強的鎮靜效果 4. 建議給予相對較大的夜間劑量以模仿睡眠周期
	Haloperidol	起始劑量: 0.5-5 mg IV 增加劑量: 每15-30 分鐘，可重複給予bolus dose 或加倍起初的bolus dose 直到病人穩定。然後可以開始每 6 小時給予最後使病人穩定下來的bolus dose的25%劑量 最大劑量: 10 mg IV	1. 在使用scheduled quetiapine的病人，可加上haloperidol 作為突發性躁動的prn 使用 2. 相對較多的extrapyramidalsymptoms (EPS) and QTcprolongation 3. 盡量避免使用於本身有QTc prolongation, 併用可導致QTc prolonging 的藥物, 或有心律不整的病患。 4. 避免突然停藥: 每天逐漸減低 haloperidol 劑量

PICO

Should dexmedetomidine, when compared with propofol, be used for sedation in critically ill, mechanically ventilated adults?

PICO

問題/研究族群 Problem/Patient	Patients with sepsis and mechanical ventilator use
給予的措施 Intervention	Dexmedetomidine
對照組 Comparison	Propofol
結果 Outcome	Efficacy: sedation (RASS) , delirium Safety: vital sign

Clinical appraisal

ORIGINAL ARTICLE

Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

C.G. Hughes, P.T. Mailloux, J.W. Devlin, J.T. Swan, R.D. Sanders, A. Anzueto, J.C. Jackson, A.S. Hoskins, B.T. Pun, O.M. Orun, R. Raman, J.L. Stollings, A.L. Kiehl, M.S. Duprey, L.N. Bui, H.R. O'Neal, Jr., A. Snyder, M.A. Gropper, K.K. Guntupalli, G.J. Stashenko, M.B. Patel, N.E. Brummel, T.D. Girard, R.S. Dittus, G.R. Bernard, E.W. Ely, and P.P. Pandharipande, for the MENDS2 Study Investigators*

Study design

- **double-blind, randomized, controlled trial (1:1=dex:pro)**
  - 13 medical centers in the United States
  - Stratified randomization: site, age (cutpoint:65 years old)
- Inclusion criteria:
  - **Adults had suspected/known infection and with continuous sedation for invasive mechanical ventilation in medical/surgical intensive care unit**
- Exclusion criteria:
  - Baseline severe cognitive impairment (Blind, deaf)
  - Pregnant or breast-feeding
  - **Second or third-degree heart block / Persistent bradycardia (need meds)**
  - Known allergy to dexmedetomidine or propofol
  - **Had an indication for benzodiazepines**
  - **Mechanical ventilator: immediate discontinuation or already use >96hr**
  - **Expected neuromuscular blockade > 48 hours**

Double blind

1. Place 3 foot blinding sleeve loosely on IV tubing that goes from medication to above pump before priming.

2. Spike Study drug bag and prime tubing.

3. Cover study bag with blinding bag cover.

4. Tape 3 foot sleeve to IV bag & tape sleeve down to section right before it goes into pump.

5. Do not place any blinding sleeves in pump

6. Slide 6 foot sleeve on lower aspect of tubing & tape sleeve on either end to cover all tubing from pump to patient.

Special Notes

- Call Pharmacy 2 hours prior to needing a new IV bag.
- Change IV bags & tubing every 12 hours.
- Extra sleeves are available for extensions.

Double blind

Identical IV fluid bags tubing covered with opaque plastic bags

- 5 to 50 µg /kg/min (actual body weight) Propofol
- 0.15 to 1.5 µg/kg /hr (actual body weight) dexmedetomidine

MENDS2

Propofol (mcg/kg/min)	5	10	15	20	25	30	35	40	45	50
Dexmedetomidine (mcg/kg/hr)	0.15	0.30	0.45	0.60	0.75	0.90	1.05	1.20	1.35	1.50

		Infusion Rate (ml/hr)									
Patient Weight (kg)	40	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
	45	1.4	2.7	4.1	5.4	6.8	8.1	9.5	10.8	12.2	13.5
	50	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0
	55	1.7	3.3	5.0	6.6	8.3	9.9	11.6	13.2	14.9	16.5
	60	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4	16.2	18.0
	65	2.0	3.9	5.9	7.8	9.8	11.7	13.7	15.6	17.6	19.5
	70	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8	18.9	21.0
	75	2.3	4.5	6.8	9.0	11.3	13.5	15.8	18.0	20.3	22.5
	80	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2	21.6	24.0
	85	2.6	5.1	7.7	10.2	12.8	15.3	17.9	20.4	23.0	25.5
	90	2.7	5.4	8.1	10.8	13.5	16.2	18.9	21.6	24.3	27.0
	95	2.9	5.7	8.6	11.4	14.3	17.1	20.0	22.8	25.7	28.5
	100	3.0	6.0	9.0	12.0	15.0	18.0	21.0	24.0	27.0	30.0
	105	3.2	6.3	9.5	12.6	15.8	18.9	22.1	25.2	28.4	31.5
	110	3.3	6.6	9.9	13.2	16.5	19.8	23.1	26.4	29.7	33.0
	115	3.5	6.9	10.4	13.8	17.3	20.7	24.2	27.6	31.1	34.5
	120	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8	32.4	36.0
	125	3.8	7.5	11.3	15.0	18.8	22.5	26.3	30.0	33.8	37.5
	130	3.9	7.8	11.7	15.6	19.5	23.4	27.3	31.2	35.1	39.0
	135	4.1	8.1	12.2	16.2	20.3	24.3	28.4	32.4	36.5	40.5
	140	4.2	8.4	12.6	16.8	21.0	25.2	29.4	33.6	37.8	42.0

Trial intervention

- Scale : **twice per day in ICU stay**
  - RASS 0 to -2 : light sedation, adjust dose every 10min
  - CAM-ICU (confusion assessment) : (+) indicates delirium
  - CPOT : for pain (use opioid bolus/ fentanyl pump)
- Temporary hold trial drug if:
  -

Adverse event

- BP, HR↓
- Deeper sedation than target

Treatment need

- Spontaneous awakening trials
- Surgery

Trial intervention

- Permanent discontinuation trial drug if:

Heart

Symptomatic bradycardia

New onset

2-3 degree AV block

Adverse event

Allergic reaction

Propofol infusion syndrome

Severe

adverse event

Trial intervention

- Discontinuation criteria (end)
  - 14-day intervention period
  - Extubation : If reintubation within 14 days, resume trial drug
  - ICU discharge

- Cognition evaluation 6months after randomization
  - TICS : Telephone Interview for Cognitive Status
  - ADL :Katz Activities of Daily Living (ADL) scale
  - FAQ: Functional Activities Questionnaire
  - EQ-5D : European Quality of Life–5 Dimensions

Trial

MENDS2

Rescue Protocol

PAIN

- First try to treat with **intermittent boluses of 0.5-1 mcg/kg of fentanyl** or other opiates such as morphine or hydromorphone
- If needed, continuous fentanyl infusions may be used

RESCUE SEDATION

- **If on max study drug & still undersedated** first try additional **intermittent opiates** (e.g. fentanyl, morphine, hydromorphone) **or increase the continuous fentanyl infusion**
- **If on max study drug & cont fentanyl** is ≥ 4-5 mcg/kg/hr & pt is still undersedated use **intermittent dose midazolam**

CHEMICAL PARALYSIS

- **Midazolam** intermittent or via continuous infusion may be used
- Reduce study drug to the **lowest infusion rate** on the weight based titation table & maintain at this level during chemical paralysis
- **Continuous midazolam** infusions should be dc'd 1 hour after the paralytic infusion is dc'd & study drug titration should resume per protocol
- When a bolus of chemical paralysis is required for procedures, **intermittent midazolam** or **propofol** will be permitted to provide amnesia

HYPERACTIVE DELIRIUM

Defined as CAM-ICU + and RASS +1 to +4

- May give **haloperidol** per tube or as 2-5mg IV intermittent doses
- **Quetiapine** (oral or per tube) prn or scheduled with recommended starting doses of 25-50 mg & titration per primary team
- **ABCDE Bundle** Nonpharmalocigal interventions such as early mobility if passes safety screen

Study design

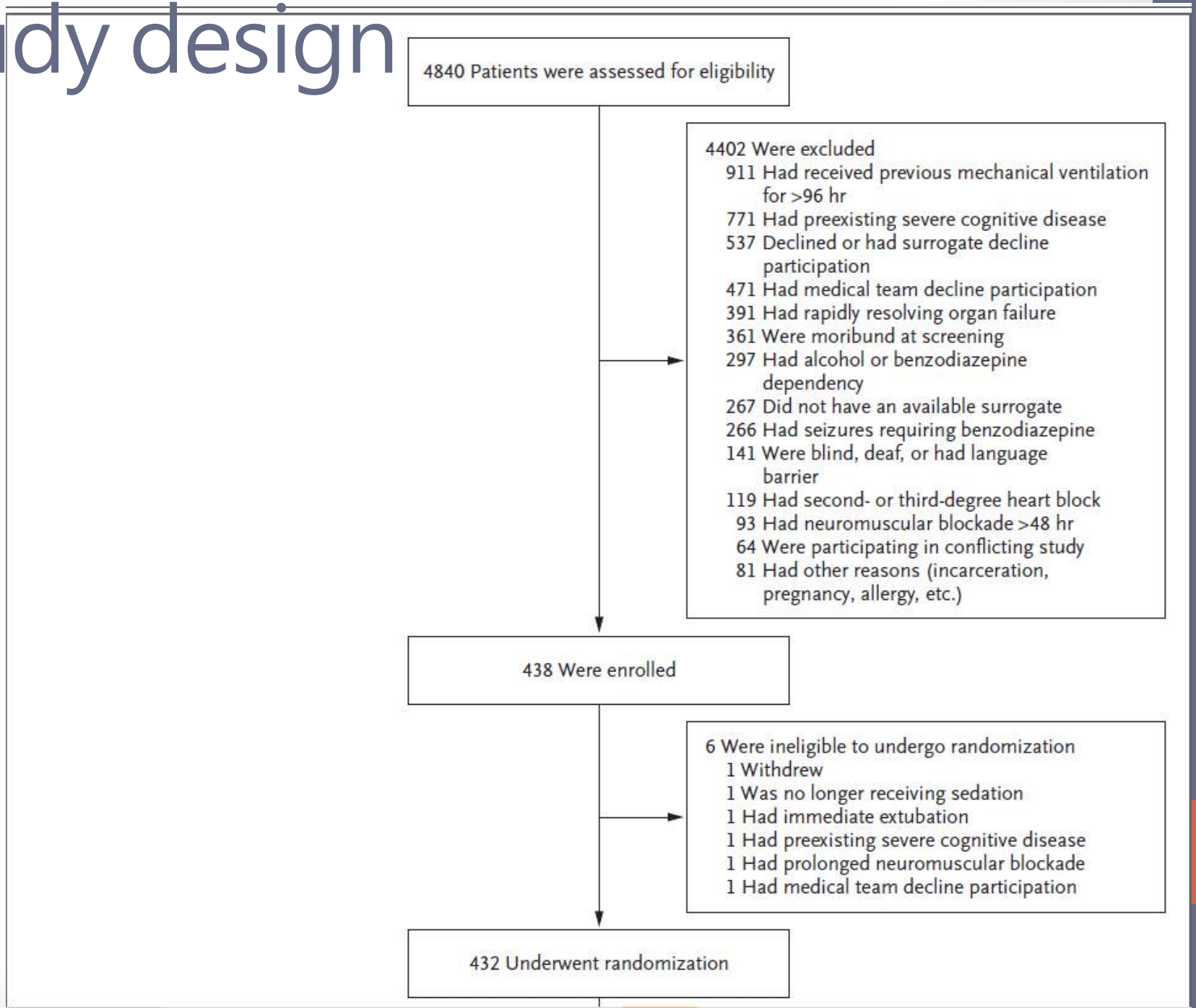
1. Short term : **14 days** period after randomization
2. Long term: 6 months after randomization (cognition)

Primary Endpoint	**days alive without delirium or coma during the 14-day study intervention period**
Secondary outcome	Ventilator-free days at 28 days Death at 90 days Global cognition at 6 months
Safety	Organ dysfunction, hypotension, brady/tachycardia Severe lactic acidosis, ARDS, withdrawal

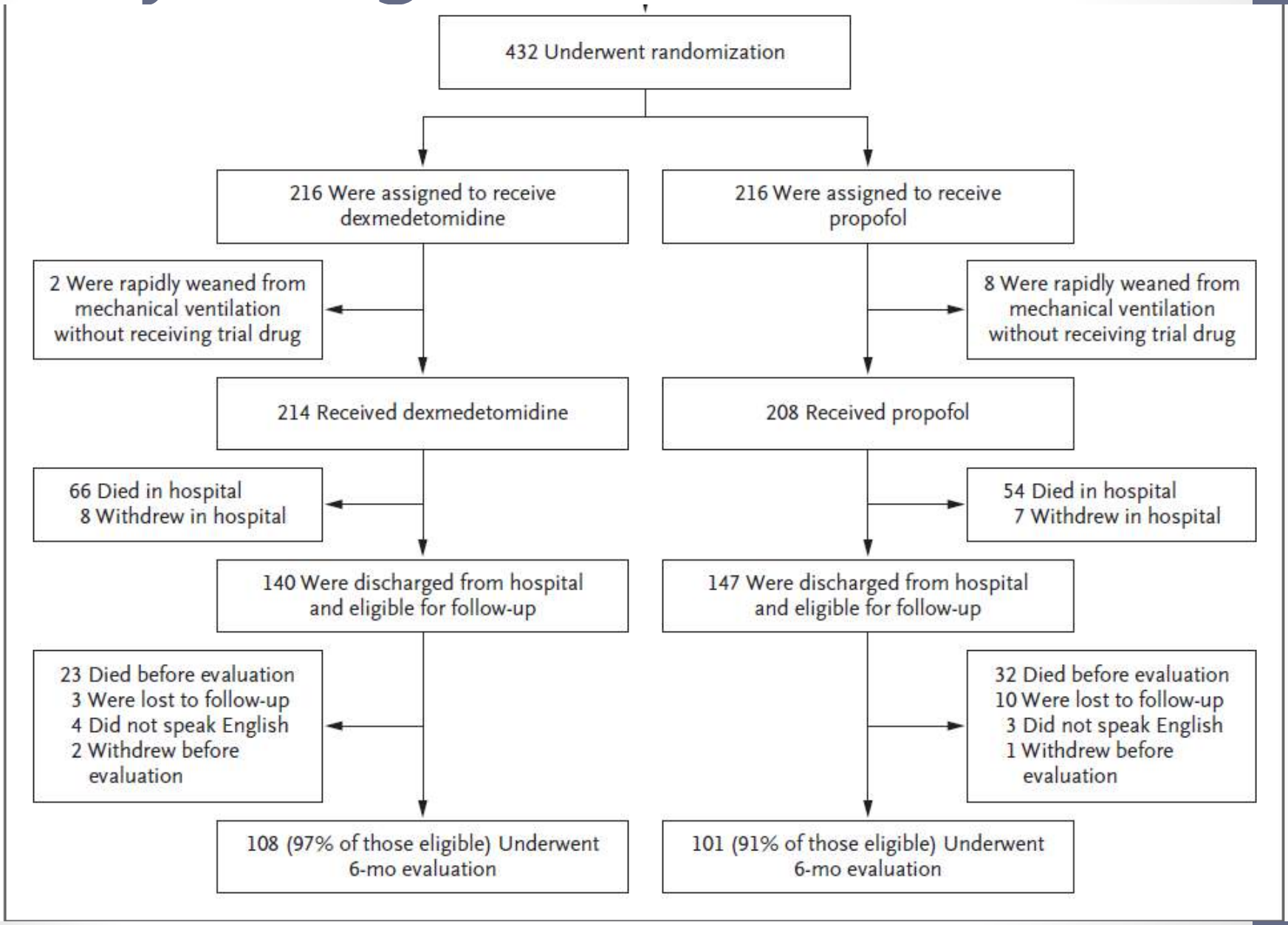
Statistical analysis

- Modified Intention to treat
- 530→420 patients :
  - Provide 85% power to detect a 1.5 day difference in days alive without delirium or coma
  - Provide 80% power to detect a 12 percentage-point absolute difference in mortality at 90 days
  - Provide at least 80% power to detect a 3.9-point difference in age-adjusted TICS-T scores between groups
- Univariate/ Multivariable regression
- Statistically significance
  - primary end point analysis to $P<0.044$
  - all other end points was $P<0.05$

Study design



Study design



Baseline characteristic

Characteristic	Dexmedetomidine (N = 214)	Propofol (N = 208)
Median age (IQR) — yr	59 (48–68)	60 (50–68)
Female sex — no. (%)	93 (43)	88 (42)
Median body-mass index (IQR)†	30 (25–38)	29 (25–37)
Race or ethnic group — no. (%)‡		
White	188 (88)	177 (85)
Black	15 (7)	23 (11)
Latinx	12 (6)	18 (9)
Multiple or other	11 (5)	8 (4)
Median IQCODE-SF score (IQR)§	3.06 (3.00–3.23)	3.00 (3.00–3.25)
Median Charlson Comorbidities Index score (IQR)¶	2 (1–4)	2 (1–4)
Admitted to surgical ICU — no. (%)	76 (36)	72 (35)
Median APACHE II score at ICU admission (IQR)‖	27 (21–32)	27 (22–32)
Median days from ICU admission to trial enrollment (IQR)	1.21 (0.67–1.95)	1.17 (0.68–1.94)
Median days of mechanical ventilation before trial enrollment (IQR)	0.98 (0.58–1.36)	0.97 (0.61–1.54)
Median total SOFA score at trial enrollment (IQR)**	10 (8–13)	10 (8–12)
Shock, receiving vasopressor, at enrollment — no. (%)	119 (56)	102 (49)
Known or suspected source of infection — no. (%)		
Blood	92 (43)	79 (38)
Lung	116 (54)	133 (64)
Abdomen	19 (9)	20 (10)
Urinary tract	46 (21)	55 (26)
Skin or wound	23 (11)	26 (12)
Stool	12 (6)	12 (6)
Other	24 (11)	21 (10)
Infection status — no. (%)		
Infection confirmed by culture	146 (68)	132 (63)
Infection suspected but not confirmed by culture	58 (27)	68 (33)
Infection ruled out	10 (5)	8 (4)

Baseline characteristic

Characteristic	Dexmedetomidine (N=214)	Propofol (N=208)
Dexmedetomidine before enrollment — no. (%)	35 (16)	25 (12)
Propofol before enrollment — no. (%)	131 (61)	129 (62)
Benzodiazepine before enrollment — no. (%)	62 (29)	73 (35)
Opioid before enrollment — no. (%)	144 (67)	147 (71)
Antipsychotic agent before enrollment — no. (%)	24 (11)	27 (13)
Delirium at enrollment — no. (%)††	75 (35)	91 (44)
Level of arousal closest to the time of randomization — no. (%)‡‡		
Coma: RASS −5 or −4	81 (38)	74 (36)
Deep sedation: RASS −3	29 (14)	38 (18)
Light sedation: RASS −2 or −1	85 (40)	75 (36)
Awake and calm: RASS 0	13 (6)	14 (7)
Agitated: RASS +1 to +4	6 (3)	7 (3)

Adherence

Table 2. Adherence and Sedation Regimen.

Outcome	Dexmedetomidine N=214	Propofol N=208
Median hours from meeting inclusion criteria to drug initiation (IQR)	22.4 (13.4–31.3)	22.1 (12.8–33.7)
Median hours from randomization to drug initiation (IQR)	1.3 (0.9–2.2)	1.3 (0.8–2.1)
Trial drug administration		
Median days of receipt of drug (IQR)	3.0 (2.0–5.0)	4.0 (2.0–6.0)
Median days from first meeting trial criteria to initiation of drug (IQR)	1.00 (0.00–1.00)	1.00 (0.00–1.00)
Median daily volume on days administered (IQR) — ml	119 (46–243)	131 (67–229)
Median daily dose on days administered (IQR)	0.27 μg/kg/hr (0.11–0.61)	10.2 μg/kg/min (5.5–18.4)
Median total no. of drug adjustments per patient (IQR)	9 (5–15.8)	11.5 (5.8–25)
Drug temporarily held — no. (%)*	60 (28)	57 (27)
Median no. of times drug temporarily held per patient (IQR)	1 (1–1)	1 (1–2)
Drug permanently discontinued — no. (%)	25 (12)	23 (11)
Trial or clinical team aware of the drug used — no. (%)	27 (13)	31 (15)
Withdrawal from trial during hospitalization — no. (%)	10 (5)	9 (4)
Median RASS score while receiving drug (IQR)	−2.00 (−3.00 to −1.00)	−1.95 (−3.03 to −0.98)
Percent time at target sedation level while receiving drug	57	60
Median CPOT score while receiving drug (IQR)†	0.33 (0.00–0.83)	0.31 (0.00–0.87)
Percent of days with adherence to ABCDE bundle‡		
Spontaneous awakening trial	98	98
Spontaneous breathing trial	93	95
Coordination of awakening and breathing trials	86	84
Nondrug delirium interventions	99	99
Early mobilization	91	92

Adherence

Table 2. Adherence and Sedation Regimen.

Outcome	Dexmedetomidine N = 214	Propofol N = 208
Midazolam exposure		
Ever used — no. (%)	114 (53)	90 (43)
Median days among users (IQR)	2.0 (1.0–4.0)	1.0 (1.0–2.0)
Median daily dose on days administered (IQR) — mg per day	3.8 (2.0–10.9)	4.0 (2.0–10.8)
Antipsychotic exposure		
Ever used — no. (%)	90 (42)	87 (42)
Median days among users (IQR)	5.0 (2.0–7.8)	4.0 (2.0–8.0)
Median daily dose on days administered (IQR) — mg§	2.2 (1.0–6.4)	3.6 (1.0–6.3)
Open-label propofol exposure		
Ever used — no. (%)	27 (13)	16 (8)
Median days among users (IQR)	2.0 (1.0–3.0)	1.5 (1.0–2.0)
Median daily dose on days administered (IQR) — μg/kg/min	10.8 (4.9–17.4)	4.8 (3.4–6.6)
Open-label dexmedetomidine exposure		
Ever used — no. (%)	9 (4)	6 (3)
Median days among users (IQR)	1.0 (1.0–2.0)	1.0 (1.0–3.2)
Median daily dose on days administered (IQR) — μg/kg/hr	0.24 (0.04–0.30)	0.26 (0.07–0.7)

Table S2. Additional adherence and sedation regimen by treatment group

Outcome	Dexmedetomidine N=214	Propofol N=208
Median daily trial drug amount on days administered [IQR]*	594 [231-1216]	1311 [668-2290]
Median number of upward trial drug titrations per patient [IQR]	4.5 [2-9.8]	6 [3-12]
Reason for upward titration—no. (%)		
Undersedation	173 (82%)	171 (82%)
Restart after SAT	43 (20%)	72 (35%)
Discontinuation of NMB	4 (2%)	4 (2%)
Median number of downward trial drug titrations per patient [IQR]	4 [2-8]	6 [3-12]
Reason for downward titration—no. (%)		
Oversedation	131 (63%)	163 (80%)
Hypotension	95 (46%)	90 (44%)
No sedation required	60 (29%)	62 (30%)
Bradycardia	53 (26%)	19 (9%)
NMB infusion	5 (2%)	3 (2%)

Table S2. Additional adherence and sedation regimen by treatment group

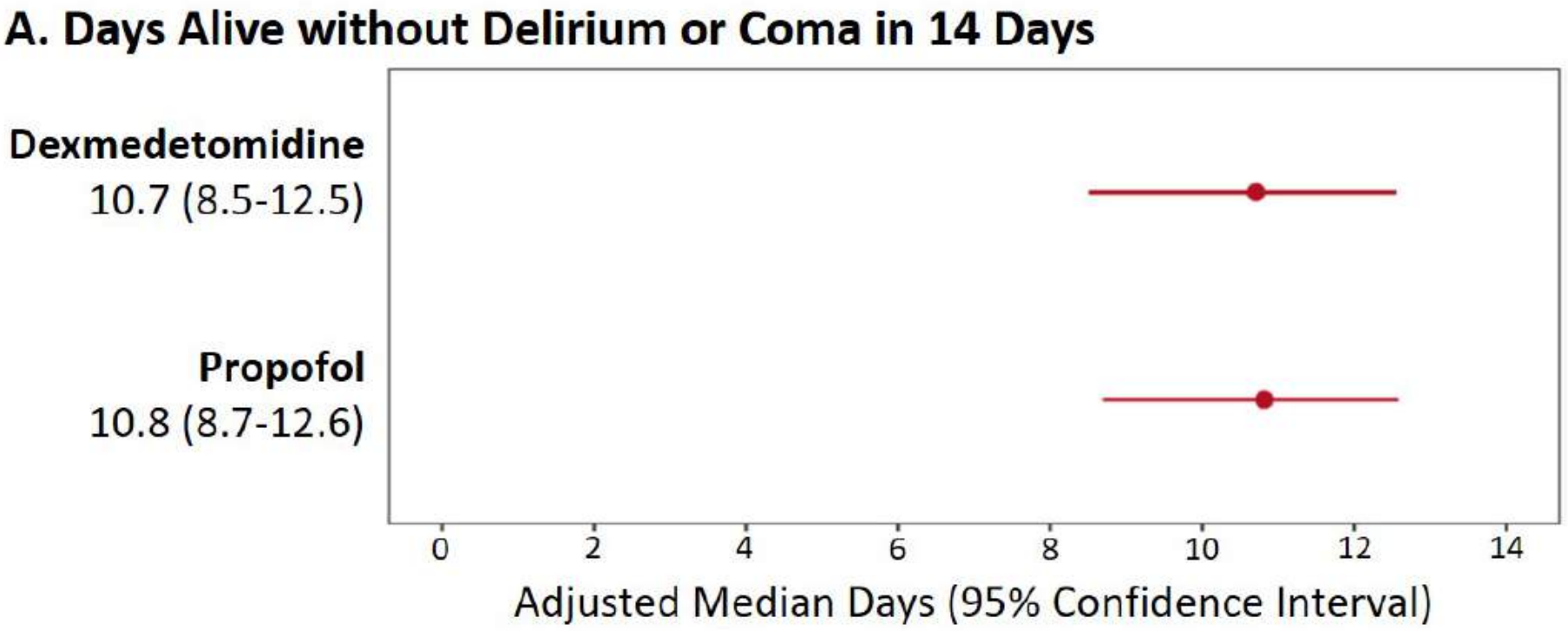
Outcome	Dexmedetomidine N=214	Propofol N=208
Temporary hold of trial drug†		
Number of patients—no. (%)	60 (28%)	57 (27%)
Median times temporarily held per patient [IQR]	1 [1-1]	1 [1-2]
Reason for temporary hold—no. (%)		
Oversedation	27 (14%)	38 (20%)
Hypotension	40 (21%)	29 (15%)
Bradycardia	24 (12%)	4 (2%)
Permanent discontinuation of trial drug		
Number of patients—no. (%)	25 (12%)	23 (11%)
Reason for discontinuation—no. (%)		
Symptomatic bradycardia	4 (2%)	3 (1%)
New structural brain disease	0 (0%)	1 (0%)
Suspected PRIS	0 (0%)	1 (0%)
Withdrawal from treatment	21 (10%)	18 (9%)

Primary/secondary outcome

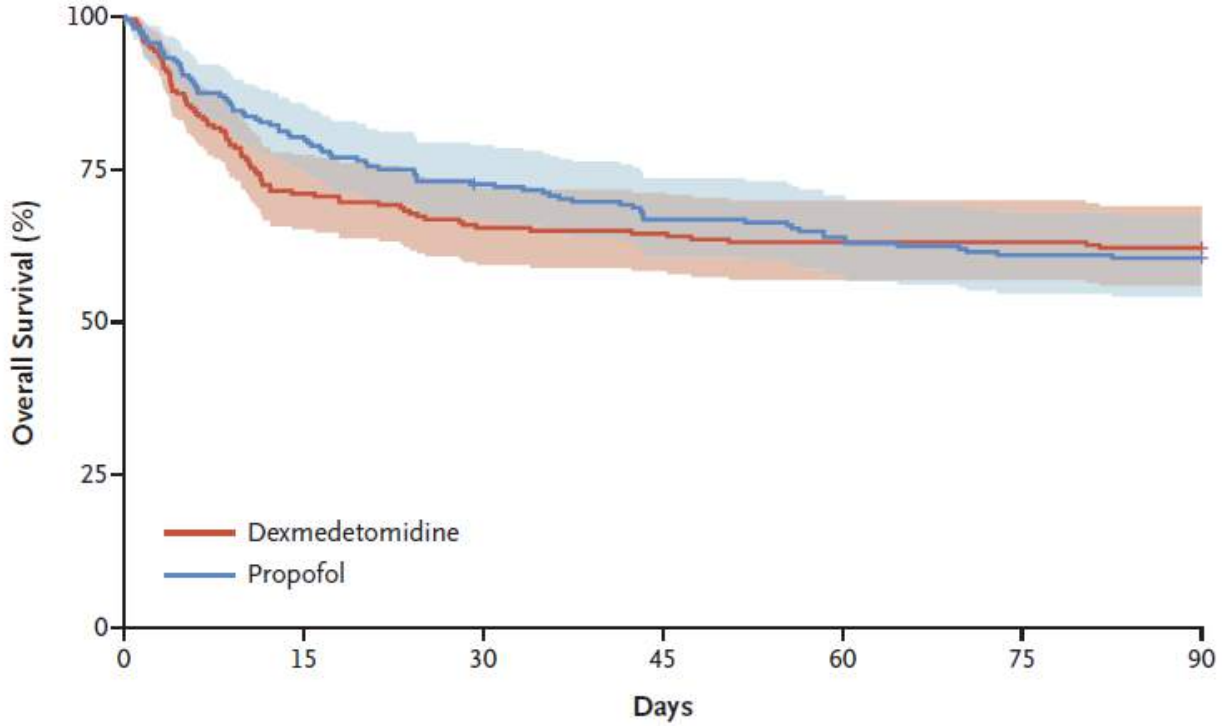
Table 3. Primary and Secondary Efficacy End Points.*

End Point	Dexmedetomidine (N=214)	Propofol (N=208)
Primary end point		
Days alive without delirium or coma at 14 days		
Unadjusted no. of days — median (IQR)	8.0 (1.0–12.8)	7.5 (1.8–11.2)
Adjusted no. of days — median (95% CI)	10.7 (8.5–12.5)	10.8 (8.7–12.6)
Adjusted odds ratio (95% CI)	0.96 (0.74–1.26)	Reference
Secondary end points		
Ventilator-free days at 28 days		
Unadjusted no. of days — median (IQR)	20.9 (0.0–26.1)	19.9 (4.2–24.9)
Adjusted no. days — median (95% CI)	23.7 (20.5–25.4)	24.0 (20.9–25.4)
Adjusted odds ratio (95% CI)	0.98 (0.63–1.51)	Reference
Death at 90 days		
Unadjusted no. of patients (%)	81 (38)	82 (39)
Adjusted hazard ratio (95% CI)	1.06 (0.74–1.52)	Reference
TICS-T score at 6 mo†		
Unadjusted score — median (IQR)	39 (28–48)	38 (30–46)
Adjusted score — median (95% CI)	40.9 (33.6–47.1)	41.4 (34.0–47.3)
Adjusted odds ratio (95% CI)	0.94 (0.66–1.33)	Reference

Primary outcome



Secondary outcome

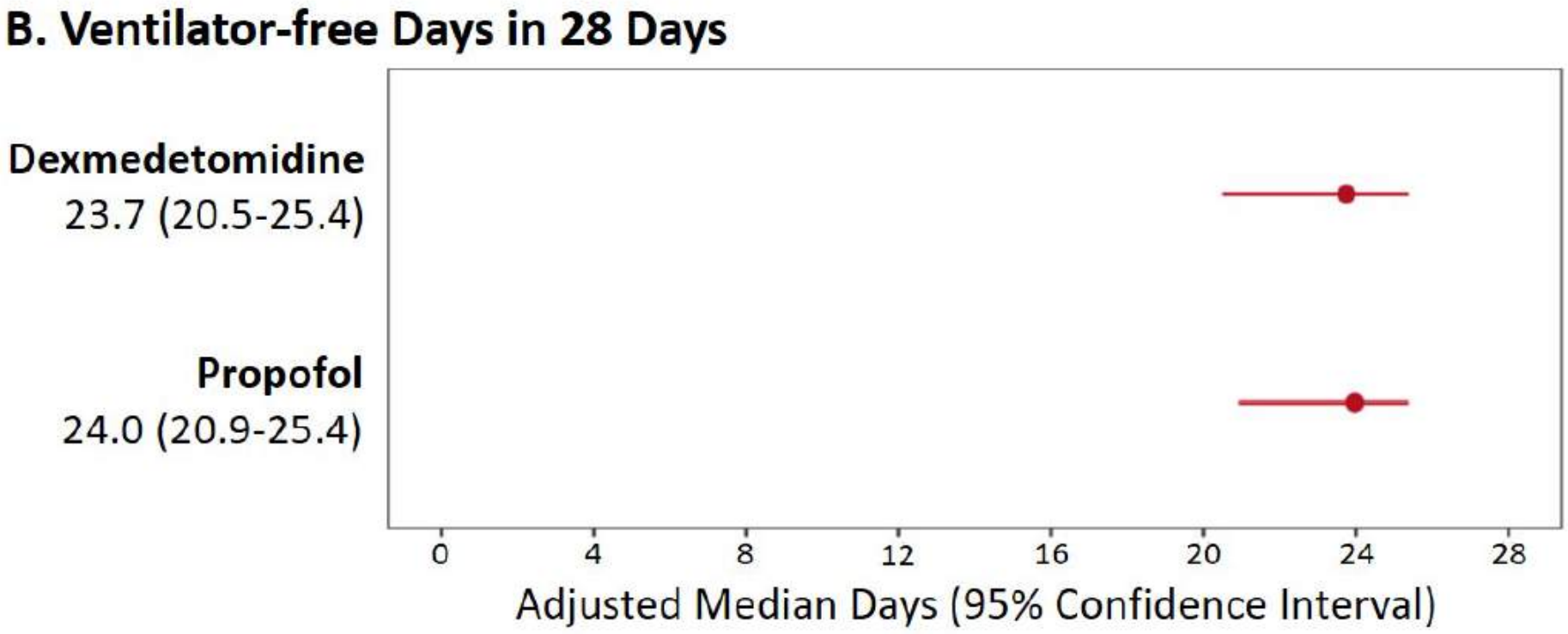


No. at Risk (Cumulative No. of Deaths)							
Dexmedetomidine	214 (0)	152 (62)	140 (74)	138 (76)	135 (79)	135 (79)	133 (81)
Propofol	208 (0)	167 (41)	150 (57)	138 (69)	132 (75)	126 (81)	125 (82)

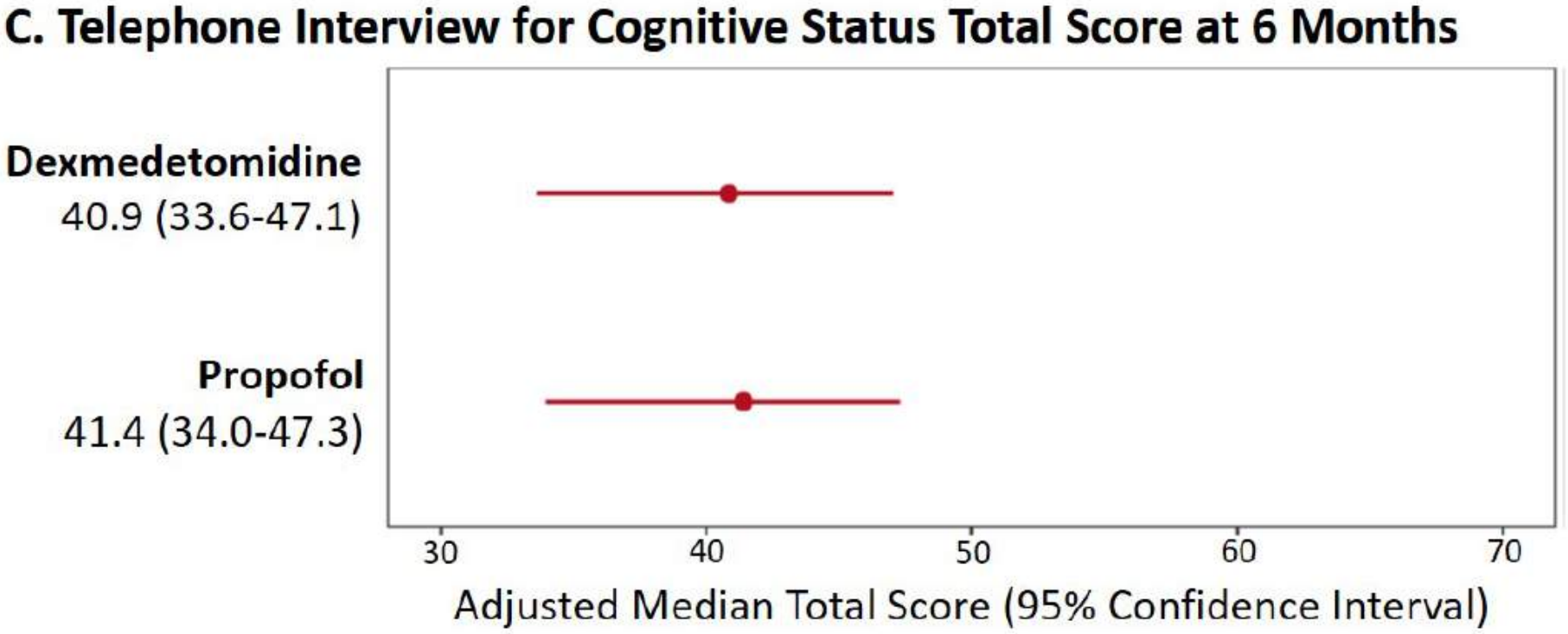
Figure 2. Effects of Dexmedetomidine and Propofol on 90-Day Survival.

The Kaplan–Meier method was used to estimate the probability of survival. In the adjusted analyses, there was no significant difference between the trial groups with respect to death at 90 days (hazard ratio with dexmedetomidine vs. propofol, 1.06; 95% confidence interval [CI], 0.74 to 1.52). Results have not been adjusted for multiple comparisons. The shading indicates 95% confidence intervals.

Secondary outcome



Secondary outcome



Safety outcome

Table S6. Organ dysfunction during 14-day study period by treatment group*		
Organ System	**Dexmedetomidine N=214**	**Propofol N=208**
Cardiovascular—no. (%)	143 (67%)	134 (64%)
Coagulation—no. (%)	83 (39%)	88 (42%)
Hepatic—no. (%)	48 (22%)	44 (21%)
Renal—no. (%)	105 (49%)	87 (42%)
Respiratory—no. (%)	211 (99%)	207 (100%)

* We defined organ dysfunction as: Cardiovascular, need for vasopressor (SOFA ≥2); Coagulation, platelet count < 100,000/mm3; Hepatic, total bilirubin > 2 mg/dL; Renal, Cr > 2 mg/dL; Respiratory, PaO_2/FiO_2 <300 or SaO_2/FiO_2 <315.

Safety outcome

Table S7. Safety end points during 14-day study period by treatment group

End point	Dexmedetomidine N=214	Propofol N=208
Hypotension (SBP<80 mm Hg)—no. (%)	119 (56%)	115 (55%)
Median CV SOFA score [IQR]	0.91 [0.43-1.98]	1.00 [0.50-1.44]
Proportion of days CV SOFA≥2—(%)	25%	21%
Bradycardia (HR<60 bpm)—no. (%)	65 (30%)	39 (19%)
Tachycardia (HR>100 bpm)—no. (%)	163 (76%)	165 (79%)
Severe lactic acidosis (>5 mmol/L)—no. (%)	31 (14%)	30 (14%)
ARDS—no. (%)	111 (52%)	135 (65%)
Signs of trial drug withdrawal—no. (%)*	22 (10%)	36 (17%)
Self extubation		
Ever occurred while on trial drug— no. (%)	13 (6%)	5 (2%)
Required re-intubation on same day— no. (%)	5 (39%)	1 (20%)

Safety outcome

Table S7. Safety end points during 14-day study period by treatment group

End point	Dexmedetomidine N=214	Propofol N=208
Triglycerides		
Median level day 7 [IQR]	140 [98-202]	166 [112-254]
Level >500 mg/dL on day 7†	3/159	6/164
Median level day 14 [IQR]	132 [101-198]	151 [109-216]
Level >500 mg/dL on day 14†	1/71	6/96
Cortisol		
Median level day 7 [IQR]	13.0 [7.8-17.9]	13.2 [9.0-18.6]
Level <20 mcg/dL on day 7†	132/159	126/161
Median level day 14 [IQR]	11.7 [8.0-16.6]	13.6 [9.0-18.7]
Level <20 mcg/dL on day 14†	64/71	72/94

Discussion

- **No significant in primary/secondary outcome**
  - Alive days without brain dysfunction
  - Ventilator-free days at 28 days
  - Death at 90 days
  - Global recognition at 6 months
- **More antinflammatory effect of dexmedetomidine**
  - **Cortisone level**
  - **No effect on clinical condition**

Limitation

- **14% unmasking group assignment**
  - Already higher adherence as compared with previous studies
- **Cross-contamination of sedative use**
  - Rescue protocol
- **Late initiation sedative**
  - Approximately 22hrs after enrollment in both groups
  - Limit effect on outcomes
- **Slower than anticipated enrollment**
  - Adjustments of sample size
  - Still adequate power

Conclusion

- Our trial showed that among **critically ill adults with sepsis** who were receiving **mechanical ventilation** and for whom recommended **light-sedation** approaches were used, **dexmedetomidine did not lead to better outcomes than propofol** with respect to :
  - days alive without acute brain dysfunction
  - ventilator-free days, death at 90 days
  - cognition at 6 months

CASP系統性文獻回顧檢核表

CASP
Critical Appraisal
Skills Programme

Section A: Is the basic study design valid for a randomised controlled trial?

1. Did the study address a clearly focused research question?

問題/研究族群 Problem/Patient	Patients with sepsis and mechanical ventilator use
給予的措施 Intervention	Dexmedetomidine
對照組 Comparison	Propofol
結果 Outcome	Efficacy: sedation (RASS) , delirium Safety: vital sign

CONSIDER:
Was the study designed to assess the outcomes of an intervention?
Is the research question 'focused' in terms of:

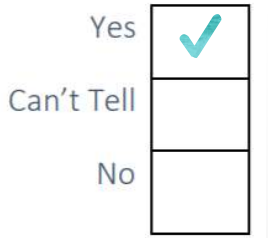
- Population studied
- Intervention given
- Comparator chosen
- Outcomes measured?

Section A: Is the basic study design valid for a randomised controlled trial?

2. Was the assignment of participants to interventions randomised?

- We randomly assigned patients to receive dexmedetomidine or propofol in a 1:1 ratio using computer-generated permuted blocks stratified by enrollment site and age (<65 years vs. ≥65 years).
- Researchers, clinicians(except bedside nurses), patients, and families were unaware of the group assignments.

HINT: Consider
CONSIDER:
• How was randomisation carried out? Wasthe method appropriate?
• Was randomisation sufficient to eliminate systematic bias?
• Was the allocation sequence concealed from investigators and participants?



Section A: Is the basic study design valid for a randomised controlled trial?

3.Were all participants who entered the study accounted for at its conclusion?

- We analyzed data in the modified intentionto- treat population, which was prespecified as all patients who underwent randomization and received a trial drug.

CONSIDER:
• Were losses to follow-up and exclusions after randomisation accounted for? • Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?
• Was the study stopped early? If so, what was the reason?

Yes	✓
Can't Tell	
No	

Section B: :Was the study methodologically sound?

4. Were the participants 'blind' to intervention they were given?

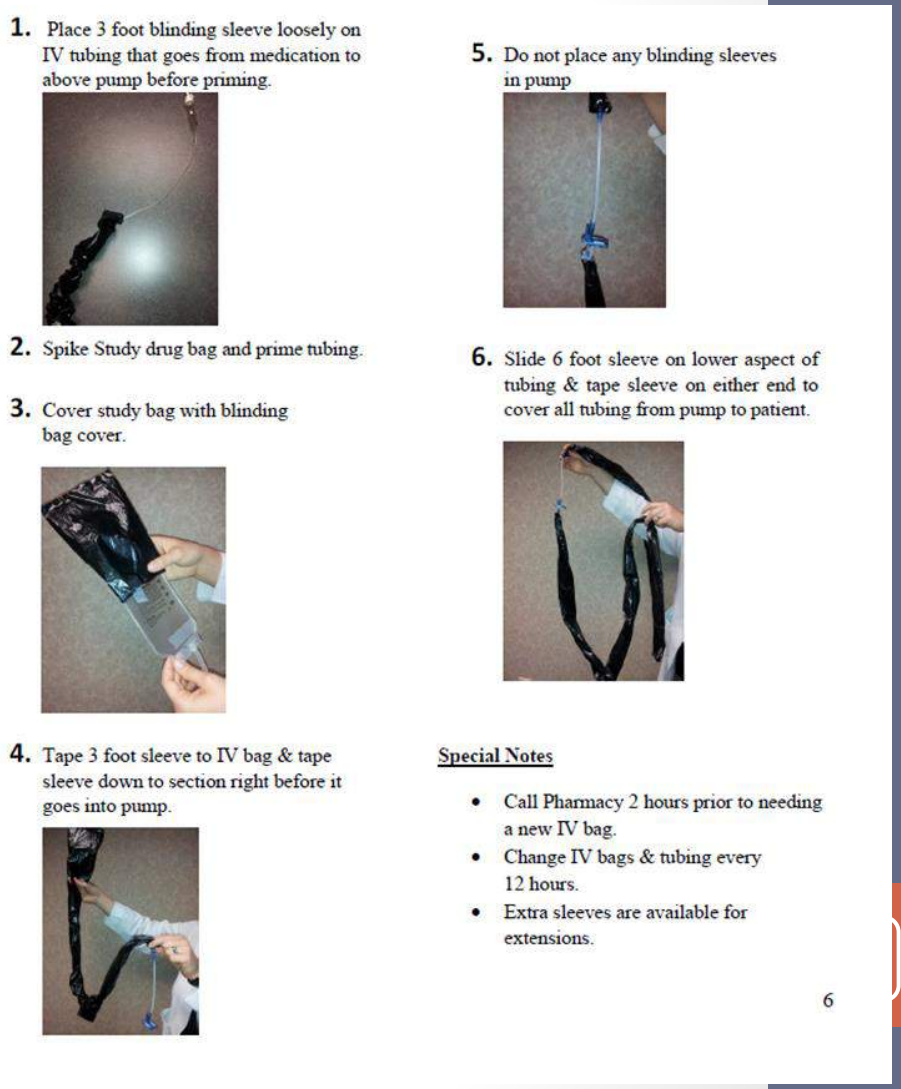
• Were the investigators 'blind' to the intervention they were giving to participants?

Yes	✓
Can't Tell	
No	

• Were the people assessing/analyzing outcome/s 'blinded'?

Yes	✓
Can't Tell	
No	

Researchers, clinicians(except bedside nurses), patients, and families were unaware of the group assignments.



1. Place 3 foot blinding sleeve loosely on IV tubing that goes from medication to above pump before priming.

2. Spike Study drug bag and prime tubing.

3. Cover study bag with blinding bag cover.

4. Tape 3 foot sleeve to IV bag & tape sleeve down to section right before it goes into pump.

5. Do not place any blinding sleeves in pump

6. Slide 6 foot sleeve on lower aspect of tubing & tape sleeve on either end to cover all tubing from pump to patient.

Special Notes

- Call Pharmacy 2 hours prior to needing a new IV bag.
- Change IV bags & tubing every 12 hours.
- Extra sleeves are available for extensions.

6

Section B: :Was the study methodologically sound?

5. Were the study groups similar at the start of the randomised controlled trial?

Yes	✓
Can't Tell	
No	

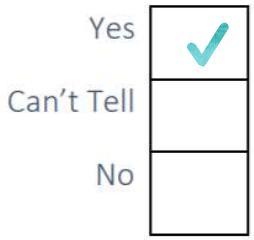
The demographic and in-hospital characteristics were similar

CONSIDER:

- ***Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?***
- ***Were there any differences between the study groups that could affect the outcome/***

Section B: :Was the study methodologically sound?

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?



- The trial drug was initially infused at a dose corresponding to the same sedative dosing that the patient was receiving immediately before randomization.
- Bedside nurses used a **weight-based dosing guideline** to adjust the trial drug every 10 minutes to target sedation goals set by the clinical team and documented each adjustment and the rationale for it.
- **Rescue protocol**

CONSIDER:

- ***Was there a clearly defined study protocol?***
- ***If any additional interventions were given (e.g. tests or treatments), were they similar between the study groups?***
- ***Were the follow-up intervals the same for each study group?***

Section C: What are the results?

7. Were the effects of intervention reported comprehensively?

Yes	✓
Can't Tell	
No	

Table 3. Primary and Secondary Efficacy End Points.*

End Point	Dexmedetomidine (N=214)	Propofol (N=208)
Primary end point		
Days alive without delirium or coma at 14 days		
Unadjusted no. of days — median (IQR)	8.0 (1.0–12.8)	7.5 (1.8–11.2)
Adjusted no. of days — median (95% CI)	10.7 (8.5–12.5)	10.8 (8.7–12.6)
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Secondary end points		
Ventilator-free days at 28 days		
Unadjusted no. of days — median (IQR)	20.9 (0.0–26.1)	19.9 (4.2–24.9)
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Unadjusted no. of patients (%)	81 (38)	82 (39)
Adjusted hazard ratio (95% CI)	1.06 (0.74–1.52)	Reference
TICS-T score at 6 mo†		
Unadjusted score — median (IQR)	39 (28–48)	38 (30–46)
Adjusted score — median (95% CI)	40.9 (33.6–47.1)	41.4 (34.0–47.3)
Adjusted odds ratio (95% CI)	0.94 (0.66–1.33)	Reference

CONSIDER:

- ***Was a power calculation undertaken?***
- ***What outcomes were measured, and werethey clearly specified?***
- ***How were the results expressed? For binary outcomes, were relative and absolute effects reported?***
- ***Were the results reported for each outcome in each study group at each follow-up interval?***
- ***Was there any missing or incomplete data?***
- ***Was there differential drop-out between the study groups that could affect the results?***
- ***Were potential sources of bias identified?***
- ***Which statistical tests were used?***
- ***Were p values reported?***

Section C: What are the results?

8. Was the precision of the estimate of the intervention or treatment effect reported?

Yes	✓
Can't Tell	
No	

CONSIDER:

- ***Were confidence intervals (CIs) reported?***

Table 3. Primary and Secondary Efficacy End Points.*

End Point	Dexmedetomidine (N=214)	Propofol (N=208)
Primary end point		
Days alive without delirium or coma at 14 days		
Unadjusted no. of days — median (IQR)	8.0 (1.0–12.8)	7.5 (1.8–11.2)
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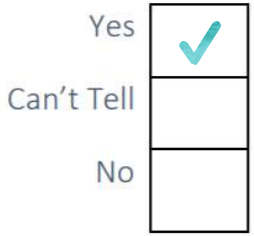
Section C: What are the results?

9. Do the benefits of the experimental intervention outweigh the harms and costs?



CONSIDER:

- ***What was the size of the intervention or treatment effect?***
- ***Were harms or unintended effects reported for each study group?***
- ***Was a cost-effectiveness analysis undertaken?***

(Cost-effectiveness analysis allows a comparison to be made between different interventions used in the care of the same condition or problem.)

Primary Endpoint	**days alive without delirium or coma during the 14-day study intervention period**
Secondary outcome	Ventilator-free days at 28 days Death at 90 days Global cognition at 6 months
Safety	Organ dysfunction, hypotension, brady/tachycardia Severe lactic acidosis, ARDS, withdrawal

Section D : Will the results help locally?

10. Can the results be applied to your local population/in your context?

Yes	
Can't Tell	✓
No	

- Patients with sepsis and mechanical ventilator support in medical /surgical intensive care unit

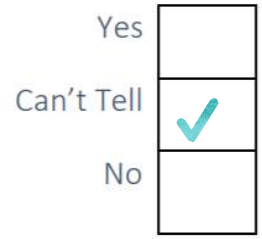
Race or ethnic group — no. (%)‡		
White	188 (88)	177 (85)
Black	15 (7)	23 (11)
Latinx	12 (6)	18 (9)
Multiple or other	11 (5)	8 (4)

CONSIDER:

- ***Are the study participants similar to the people in your care?***
- ***Would any differences between your population and the study participants alter the outcomes reported in the study?***
- ***Are the outcomes important to your population?***
- ***Are there any outcomes you would have wanted information on that have not been studied or reported?***
- ***Are there any limitations of the study that would affect your decision?***

Section D : Will the results help locally?

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?



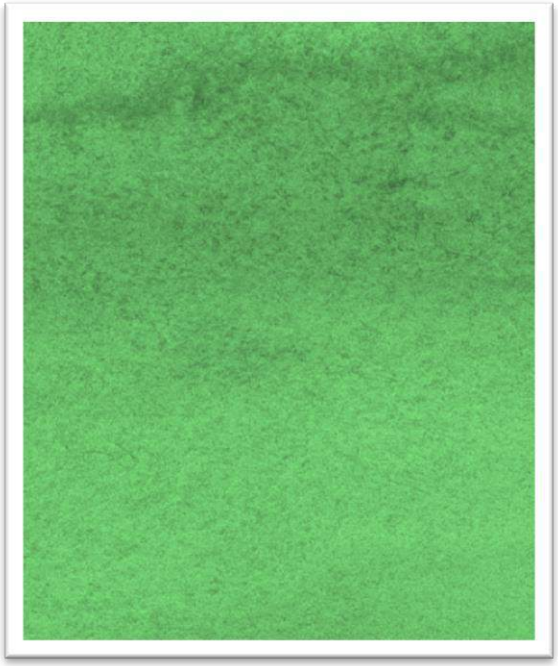
- among critically ill adults with sepsis who were receiving mechanical ventilation and for whom recommended light sedation approaches were used, **dexmedetomidine did not lead to better outcomes than propofol with respect to days alive without acute brain dysfunction, ventilator-free days, death at 90 days, or cognition at 6 months.**

CONSIDER:

- ***What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?***
- ***Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?***

在敗血症插管病人的鎮靜治療上，
dexmedetomidine 是否優於 propofol ?

同意 (綠牌)



需要更多文獻支持 (黃牌)

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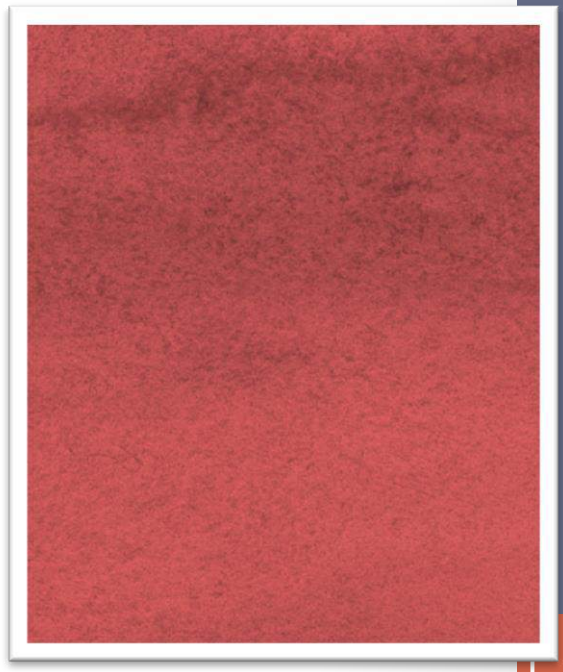


THANK YOU