Journal Meeting

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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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Acute lung injury

- Patient have a risk factor for ARDS and no history of chronic lung disease:
- ✓ Acute onset
- ✓ Bilateral infiltrates (radiographically similar to pulmonary edema)
- ✓ No evidence of elevated left atrial pressure (the pulmonary capillary wedge pressure is ≤18 mmHg if measured)
- ✓ A ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2) of 201 to 300 mmHg

Acute respiratory distress syndrome

- The PaO2/FiO2 is ≤200 mmHg

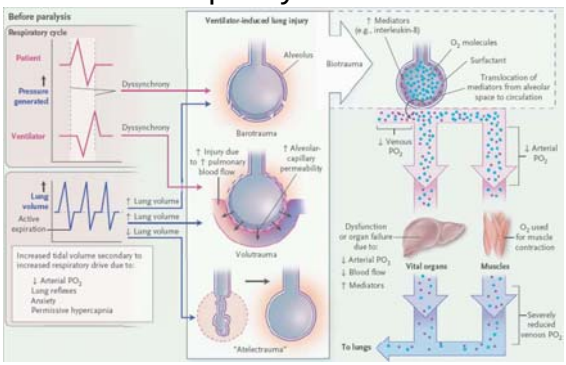
Excluding cardiogenic pulmonary edema

- Plasma brain natriuretic peptide (BNP) levels
- Echocardiography
- Right heart catheterization

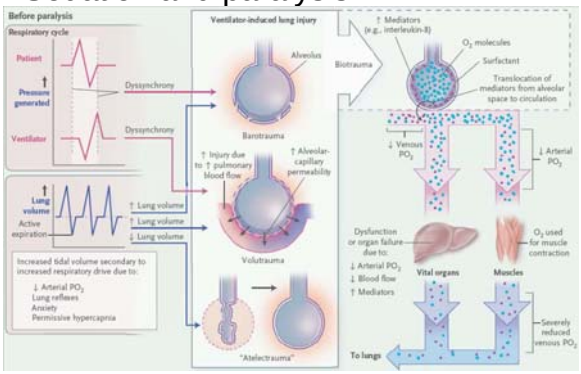
Mechanical ventilation in acute respiratory distress syndrome

- OPEN LUNG VENTILATION
- ✓ Low tidal volume ventilation :8 mL/kg IBW
- ✓ High PEEP

Sedation and paralysis



Sedation and paralysis



Background -neuromuscular blocking agents

- In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS) may:
- **improve oxygenation**
- **decrease ventilator-induced lung injury**
- **cause muscle weakness.**

Background- evaluated clinical outcomes

- 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

Methods

- Multicenter, double-blind trial
- 340 patients presenting to the ICU with an onset of severe ARDS within the previous 48 hours
- Randomly assigned to receive either **cisatracurium besylate** (178 patients) or placebo (162 patients).

ARDS

- 最初由 Ashbaughy 等人於1987年提出
- 1994年，AECC (American-European consensus conference) 正式命名定義，ARDS爲急性肺傷害 (Acute Lung Injury, ALI) 的最極端表現。
- 臨床診斷如下：(1) 急性發作 (2) 胸部X光片兩側肺浸潤 (3) 肺動脈楔壓 (Pulmonary artery wedge pressure, PAWP) ≦ 18mmHg 或無左心房高壓 (4) 氧合機能失常－PaO2／FiO2 ≦ 300mmHg 爲ALI，≦ 200mmHg 爲 ARDS。

本Trial 符合中的篩選條件

- ARDS
- PaO2/FiO2<150(severe)
- Positive end-expiratory pressure(PEEP) > 5cm H2O
- tidal volume of 6 to 8 ml per kilogram of predicted body weight.

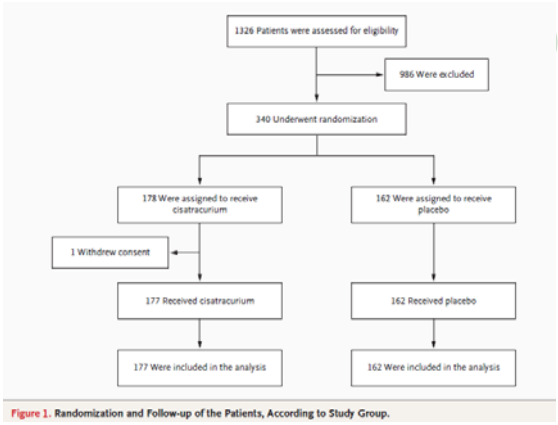


Figure 1. Randomization and Follow-up of the Patients, According to Study Group.

Data Collection

- 24-hour period before randomization
- just before starting the studydrug infusion and again at 24, 48, 72, and 96 hours.
- Physiological variables were also measured daily between 6 a.m. and 10 a.m. until day 90 or until hospital discharge of a patient who could breath spontaneously.

Study Treatment

- Once the assigned Ramsay sedation score was 6 (no response on glabellar tap)
- rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered.
- followed by a continuous infusion of 37.5 mg per hour for 48 hours.

Ramsay sedation

Score	Patient response
1	Anxious and agitated and/or restless
2	Co-operative, oriented, tranquil
3	Responds to commands only
4	Brisk response to glabellar tap/auditory stimulus
5	Sluggish response to glabellar tap/auditory stimulus
6	No response to glabellar tap/auditory stimulus

Table 1. Summary of the Ventilation Procedure.*

Variable
Ventilator mode: volume assist–control
Initial tidal volume: 6–8 ml/kg of predicted body weight
Plateau pressure: ≤32 cm of water
Oxygenation goal: PaO_2 of 55–80 mm Hg or SpO_2 of 88–95%
Permitted combinations of FiO_2 and PEEP, respectively (cm of water): 0.3 and 5, 0.4 and 5, 0.4 and 8, 0.5 and 8, 0.5 and 10, 0.6 and 10, 0.7 and 10, 0.7 and 12, 0.7 and 14, 0.8 and 14, 0.9 and 14, 0.9 and 16, 0.9 and 18, 1.0 and 18, 1.0 and 20, 1.0 and 22, and 1.0 and 24
pH goal: 7.20–7.45
Procedure when oxygenation goal not achieved despite adjustments to FiO_2 and PEEP: use inhaled nitric oxide, almitrine mesylate, prone positioning, or any combination thereof
Procedure when plateau pressure is >32 cm of water for at least 10 min (in the following order, as needed): increase sedation, reduce tidal volume to 4 ml/kg, decrease PEEP by decrements of 2 cm of water, and perform injection of cisatracurium in a bolus of 20 mg (not to be given again if plateau pressure decreased by <2 cm of water because further doses would probably be futile, but permitted if the drug had its intended effect)

Procedure to correct hypercapnia when pH is <7.20 (in the following order, as needed): connect Y-piece directly to endotracheal tube, increase respiratory rate to a maximum of 35 cycles per min, and increase tidal volume to a maximum of 8 ml/kg

Weaning attempt: starting on day 3, if FiO_2 ≤0.6

Goals during weaning procedure: SpO_2 ≥88% and respiratory rate 26–35 cycles per min

Weaning procedure: decrease PEEP over 20–30 min to 5 cm of water

Pressure-support ventilation levels used during weaning procedure: 20, 15, 10, and 5 cm of water

If weaning procedure fails at a pressure-support ventilation level of 20 cm of water, switch to volume assist–control mode of ventilation

After at least 2 hr of successful pressure-support ventilation at a level of 5 cm of water, disconnect patient from the ventilator

Study Outcomes

- *Primary Outcome*
- *Secondary Outcomes*

Primary outcome

- Proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

Secondary Outcomes

- the day-28 mortality, the numbers of days outside the ICU, days without organ or system failure,rate of barotrauma, ICU-acquired paresis, MRC scores, ventilator-free days

Results

- Baseline Characteristics
- *Primary Outcome*
- *Secondary Prespecified Outcomes*
- *Secondary Post Hoc Outcome*
- Cointerventions
- Safety

Table 2. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic†	Cisatracurium (N=177)	Placebo N=162)	P Value
Age — yr	58±16	58±15	0.70
Tidal volume — ml/kg of predicted body weight	6.55±1.12	6.48±0.92	0.52
Minute ventilation — liters/min	10.0±2.5	10.1±2.2	0.83
PEEP applied — cm of water	9.2±3.2	9.2±3.5	0.87
Plateau pressure — cm of water	25.0±5.1	24.4±4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5±11.6	31.9±10.7	0.71
FiO_2	0.79±0.19	0.77±0.20	0.33
PaO_2:FiO_2‡	106±36	115±41	0.03
pH	7.31±0.10	7.32±0.10	0.11
PaO_2 — mm Hg	80±24	85±28	0.09
$PaCO_2$ — mm Hg	47±11	47±11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50±16	47±14	0.15
Nonfatal condition according to McCabe–Jackson score — no. (%)¶	133 (75.1)	125 (77.2)	0.66
Main reason for ICU admission — no. (%)			
Medical	129 (72.9)	113 (69.8)	0.52
Surgical, emergency	27 (15.3)	31 (19.1)	0.34
Surgical, scheduled	21 (11.9)	18 (11.1)	0.83
Corticosteroids for septic shock — no. (%)	70 (39.5)	73 (45.1)	0.30
Direct lung injury — no. (%)	142 (80.2)	123 (75.9)	0.34

Primary outcome

- The hazard ratio for death at 90 days(cisatracurium group V.S placebo group) ： **0.68** (95% confidence interval [CI], 0.48 to 0.98; **P = 0.04**) after adjustment for both the baseline PaO2:FIO2 and plateau pressure and the Simplified Acute Physiology II score.
- The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (**P = 0.08**).

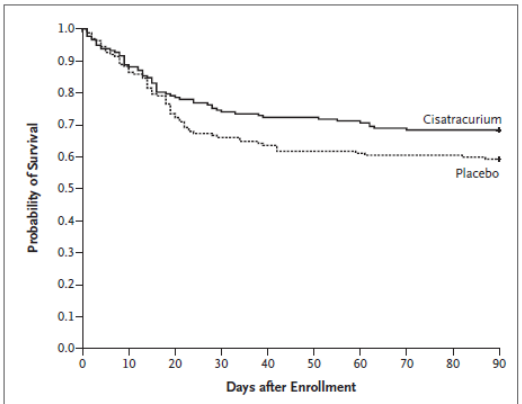


Figure 2. Probability of Survival through Day 90, According to Study Group.

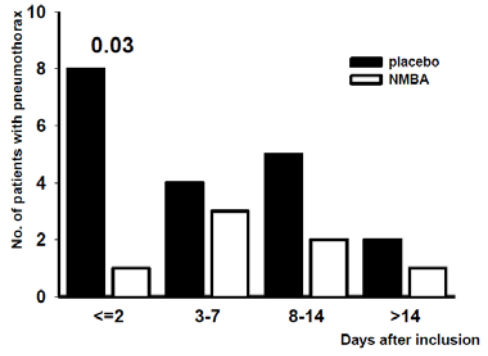
Secondary Outcomes

- Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (**P = 0.05**).
- The rate of ICU-acquired paresis did not differ significantly between the two groups.

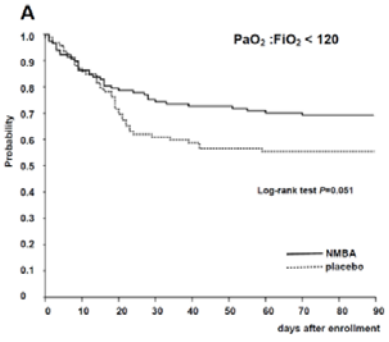
Table 3. Secondary Outcomes, According to Study Group.*

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

Secondary Prespecified Outcomes

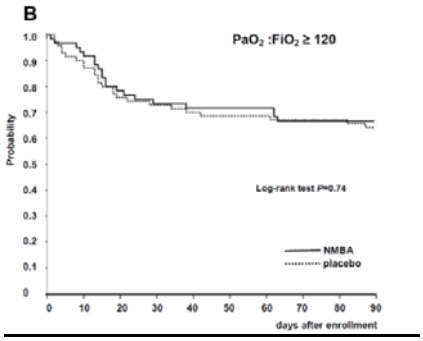


Secondary Prespecified Outcomes



- Among these patients, the 90-day mortality was 30.8% in the cisatracurium group and 44.6% in the control group (P = 0.04)

Secondary Prespecified Outcomes

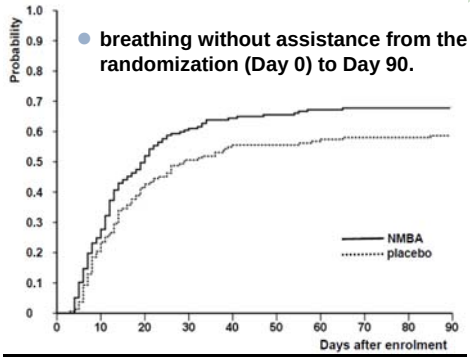


Secondary Prespecified Outcomes

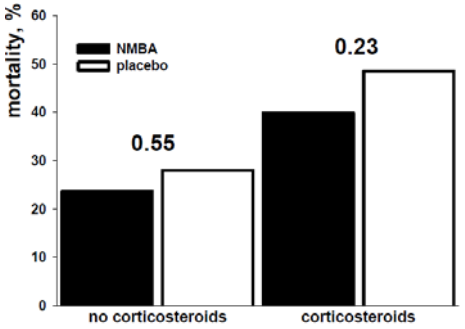
- The Cox regression model yielded an adjusted hazard ratio for weaning from mechanical ventilation by day 90, in the cisatracurium group as compared with the placebo group, of 1.41 (95% CI, 1.08 to 1.83; P = 0.01).

Secondary Prespecified Outcomes

- **breathing without assistance from the day of randomization (Day 0) to Day 90.**



Secondary Post Hoc Outcome



Corticosteroids were used during the ICU stay in 189 patients.

Cointerventions

	NMBA n = 177 *no (%)*	Placebo n= 162 *no (%)*	*P* value
Received open-label cisatracurium besylate			
During the first 48 h following inclusion	18 (10%)	36 (22%)	0.004
During the entire ICU stay including the first 48 h	89 (50%)	90 (56%)	0.33
For procedure	6 (3%)	7 (4%)	0.78
More than one administration	61 (34%)	67 (41%)	0.19
Duration (days)	1 [0-2]	1 [0-2]	0.46
Adjunctive therapies			
Prone position	50 (28%)	47 (29%)	0.88
Inhaled nitric oxide	50 (28%)	53 (33%)	0.37
Almitrine bismesylate	6 (3%)	10 (6%)	0.23
Any of the three treatments above	75 (42%)	77 (48%)	0.34
Corticosteroids for ARDS	28 (16%)	37 (23%)	0.10
Swan-Ganz catheter	40 (23%)	31 (19%)	0.43
Vasopressor	162 (92%)	144 (89%)	0.41
Dobutamine	35 (20%)	40 (25%)	0.28
Renal replacement therapy	59 (33%)	59 (36%)	0.55

NMBA denotes neuromuscular blocking agents and ARDS acute respiratory distress syndrome

Safety

- Bradycardia developed during the cisatracurium infusion in one patient.

Critical Appraisal Skills Programme (CASP)

- **10 questions to help you make sense of randomised controlled trials**

Screening Questions

1. Did the study ask a clearly-focused question? ☐Yes ☐ Can't tell ☐ No

- *Consider if the question is 'focused' in terms of:*
- *– the population studied*
- *– the intervention given*
- ***– the outcomes considered***

2. Was this a randomised controlled trial (RCT) ☐ Yes ☐ Can't tell ☐ No and was it appropriately so?

- *Consider:*
- *– why this study was carried out as an RCT*
- *– if this was the right research approach for the question being asked*

Detailed Questions

- **3. Were participants appropriately allocated intervention and control groups?**

  ☐ Yes ☐ Can't tell ☐ No

Consider:

- *how participants were allocated to intervention and control groups. Was the process truly random?*
- *whether the method of allocation was described. Was a method used to balance the randomization, e.g. stratification?*
- *how the randomization schedule was generated and how a participant was allocated to a study group*
- *if the groups were well balanced. Are any differences between the groups at entry to the trial reported?*
- *if there were differences reported that might have explained any outcome(s) (confounding)*

Detailed Questions

- **4. Were participants, staff and study personnel 'blind' to participants' study group?**

  ☐ Yes ☐ Can't tell ☐ No

Consider:

- *– the fact that blinding is not always possible*
- *– if every effort was made to achieve blinding*
- *– if you think it matters in this study*
- *– the fact that we are looking for 'observer bias'*

Study Design

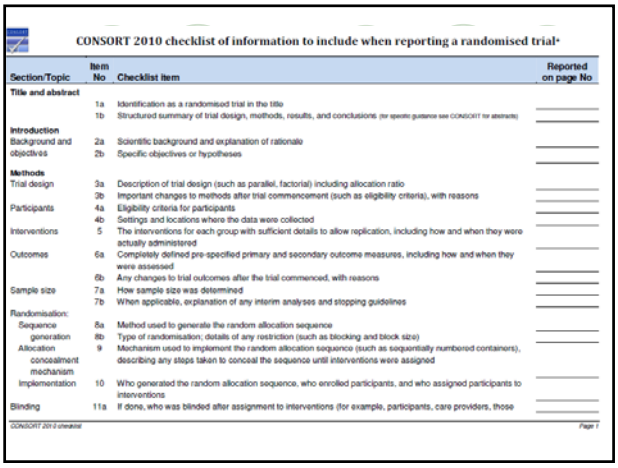
- Computer-generated random-number tables prepared by statisticians were used to assign patients in blocks of 4 to either NMBA or placebo. Patients were stratified according to center, age (≤60 years or >60 years), and mechanical ventilation duration at base-line (≤48 hours or >48 hours), yielding four groups (tables) per center.
- At each center, designated investigators enrolled the patients and called a centralized telephone system to ensure blind allocation of consecutively numbered boxes containing placebo or cisatracurium besylate.
- Patients, healthcare providers, evaluators, monitors, and data analysts were also blinded to the study treatment.

Study Design

- Randomization and blinding regarding the study-group assignments were performed according to Consolidated Standards for the Reporting of Trials (CONSORT) guidelines

CONSORT

- CONSORT（Consolidated Standards of Reporting Trials）研究檢核準則是針對隨機對照臨床試驗（RCT）的報告格式，其檢核文件（CONSORT statement）中提出25個檢查項目作爲參考。



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

CONSORT 2010 checklist Page 1

Detailed Questions

- **5. Were all of the participants who entered the trial accounted for at its conclusion?**

☐ Yes ☐ Can't tell ☐ No

Consider

- *– if any intervention-group participants got a control-group option or vice versa*
- *– if all participants were followed up in each study group (was there loss-to-follow-up?)*
- *– if all the participants' outcomes were analysed by the groups to which they were originally allocated (intention-to-treat analysis)*
- *– what additional information would you liked to have seen to make you feel better about this*

Detailed Questions

- **6. Were the participants in all groups followed up and data collected in the same way?**

☐ Yes ☐ Can't tell ☐ No

- *Consider:*
- *– if, for example, they were reviewed at the same time intervals and if they received the same amount of ttention from researchers and health workers. Any differences may introduce performance bias.*

Detailed Questions

- **7. Did the study have enough participants to minimise the play of chance?**

  ☐ Yes ☐ Can't tell ☐ No

Consider:

- *– if there is a power calculation. This will stimate how many participants are needed to be reasonably sure of finding something important (if it really exists and for a given level of uncertainty about the final result).*

Consider before study

- Assuming a 50% mortality at 90 days in the placebo group, we calculated that 340 patients would need to be enrolled to detect a 15% absolute reduction in the 90-day mortality in the cisatracurium group as compared with the placebo group, with 80% statistical power and a two-sided alpha value of 0.05.

Consider after study

- However, the mortality in the placebo group in this study (40.7%) is lower than that in the control groups in the earlier studies.
- Given the observed mortality in our placebo group,the current study was underpowered. Indeed, 885 patients would have been needed to be enrolled to achieve 80% statistical power with a two-sided alpha value of 0.05.

Detailed Questions

- **8. How are the results presented and what is the main result?**
- *– if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards*
- *– how large this size of result is and how meaningful it is*
- *– how you would sum up the bottom-line result of the trial in one sentence*

Results presented & main result

- **Means ±SD,Relative Risk,P Value**
- Adjusted 90-day survival rate ↑
- Ventilator free days ↑
- incidence of barotrauma ↓
- Overall 90-day mortality
- The rate of ICU-acquired paresis did not differ significantly

Sum up the bottom-line result of the trial in one sentence

- *size of result? meaningful ?*

- 在severe ARDS的患者，早期給予neuromuscular blocking agent可以增加adjusted survival rate且不會增加ICU-acquired paresis。

Detailed Questions

- **9. How precise are these results?**

Consider:

- *– if the result is precise enough to make a decision NO*
- *– if a confidence interval were reported.YES Would your decision about whether or not to use this intervention be the same at the upper confidence limit as at the lower confidence limit? 不知道怎麼判斷*
- *– if a p-value is reported where confidence intervals are unavailable* **NO**

10. Were all important outcomes considered so the results can be applied?

- *Consider whether:*
- *– the people included in the trail could be different from your population in ways that would produce different results*
- *– your local setting differs much from that of the trial*
- *– you can provide the same treatment in your setting*

10. Were all important outcomes considered so the results can be applied?

- *Consider outcomes from the point of view of the:*
- *– individual*
- *– policy maker and professionals*
- *– family/carers*
- *– wider community*

10. Were all important outcomes considered so the results can be applied?

- *Consider whether:*
- *– any benefit reported outweighs any harm and/or cost. If this information is not reported can it be filled in from elsewhere?*
- *– policy or practice should change as a result of the evidence contained in this trial-->NO*

老師的問題

- 1. 爲何使用RCT還會造成Table 2中兩組的baseline characteristics有差異？有差異的是哪一個特性？作者如何解決？
- PaO2:FiO2 ratio
- database不夠大?
- 利用Cox regression model來分析

Primary outcome

- The Cox regression model yielded a hazard ratio for 90-day mortality, adjusted for base-line PaO2:FIO2, SAPS II and plateau pressure, in the NMBA group versus the control group of 0.68 (CI, 0.48 to 0.98) (*P=0.04).*

Primary outcome

- Concerning the three other covariates introduced in the model, the adjusted hazard ratio for 90-day mortality for end inspiratory ventilator plateau pressure at base-line was 1.039 (CI, 1.002 to 1.077) (*P=0.04), 0.999 (CI, 0.995 to 1.004)*(*P=0.78) for base-line PaO2:FiO2, and it was 1.017 (CI, 1.006 to 1.029) (P=0.004) for* SAPS II score at base-line.
- The beneficial effect of NMBA remained after removal base-line PaO2:FiO2 from the model.
- Crude 90-day mortality was 31.6 percent (CI, 25.2;38.8) in the NMBA group and 40.7 percent (CI, 33.5;48.4) in the placebo group (*P=0.08).*

老師的問題

- 2. 何謂Prespecified secondary analyses？跟Post hoc analysis有什麼差別？好處是什麼？

Prespecified secondary analyses

- Data collected by other researcher(or previous study) can frequently be re-analyzed to answer a new problem.This kind of research, referred to as *secondary analysis,* can be undertaken with almost any kind of data, but is usually done using quantitative data from previous surveys or from reports from government ministries.

Post hoc analysis

- 爲了能進一步確認哪幾個類別樣本平均數與其他類別樣本平均數有顯著差異，我們可用事後分析（post hoc analysis）的方法。 這種事後分析方法是一一比較所有兩兩類別之間平均數的差異，然後讓我們知道是哪兩個類別間平均數的差異對於做ANOVA測定時得到之F值的貢獻最大。

老師的問題

- 3. 爲什麼作者說adjusted 90-day survival rate有統計差異，但90-day mortality沒有統計差異？

ANS:因爲baseline 有差異，所以才出現這樣的結果。

老師的問題

- 4. 如果以90-day的mortality做爲結果，而且假設有統計差異（實際上沒有）
  請問以下數值：
  a. 實驗組比上對照組的Relative Risk Reduction與Relative Risk各是多少
  b. Absolute Risk Reduction是多少？
  c. Number Needed to Treat to prevent 1 additional death是多少？
  d. 請用白話文說上題NNT的意義

Relative Risk Reduction & Relative Risk

- 對照組事件發生率 (CER, Control Event Rate)= 40.7 %
- 實驗組事件發生率 (EER, Experimental Event Rate)= 31.6 %
- 相對風險比率差 (Relative Risk Reduction) = |EER – CER| / CER= |31.6 –40.7|/ 40.7 =22.3%
- 相對危險性 (Relative Risk, RR) = EER / CER=31.6/40.7=77.6%

Absolute Risk Reduction

- 絕對風險比率差 (ARR, Absolute Risk Reduction)
- = |EER – CER| = |31.6 –40.7|=9.1

Number Needed to Treat to prevent 1 additional death是多少

- 需要被治療的病人數目 (NNT, Number Needed to Treat) = 1/ARR
- 1/ARR =1/9.1=10.98%

NNT

- 爲減少一個不良結果所需治療的病人數目