

## Continuous infusion versus intermittent bolus dosing of vecuronium in patients receiving therapeutic hypothermia after sudden cardiac arrest

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## INTRODUCTION

- 236000-325000 OHCA per year in USA
- Sudden cardiac arrest (SCA) would result in anoxic brain injury
- Therapeutic hypothermia: improve neurologic outcomes
- 50-60% of patient shiver during cooling and rewarming phases that cause:
  - Increased  $O_2$  consumption
  - Production of  $CO_2$
  - Respiratory acidosis
  - Affect myocardial oxygen balance
  - Produce heat

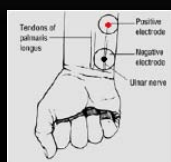
## To prevent shiver....

- Using neuromuscular blocker, e.g. vecuronium
- Vecuronium:
  - Intermediate-acting agent
  - Useful for postoperative shivering
  - Lack adverse CV effects
  - Undergo hepatic and renal clearance
- Sladen et al. in 1995
  - Patients undergoing cardiopulmonary bypass surgery
  - Vecuronium IV 0.1  $\mu\text{g}/\text{kg}$  st, then 1.0  $\mu\text{g}/\text{kg}/\text{min}$

## IN HYPOTHERMIA

- Vecuronium was used by the authors since 2004 during hypothermia therapy:
  - Cooling: Arctic Sun Cooling System (Medivance Inc., Louisville, CO)
  - Target temp:  $33^\circ\text{C}$  for 24 hours
  - Vecuronium infusion, 0.8  $\mu\text{g}/\text{kg}/\text{min}$ , started 2 hours after cooling or shivering occurred
  - Use train-of-four (TOF) test to measure the degree of NM blockade Q1H until it was consistent for 3-4 hours, then check Q2H
    - 1/4-2/4 twitches
    - If 0/4 twitches: stop vecuronium; if  $>0/4$ , start vecuronium at half the previous infusion rate
  - Discontinued vecuronium after rewarming to  $36^\circ\text{C}$

## TRAIN-OF-FOUR (TOF) TEST



- To stimulate ulnar nerve with a nerve stimulator
  - 2 Hz for 2 seconds at 0.5-second intervals
- Response: adductor pollicis muscle, i.e. thumb adduction

## NEW METHOD

- In Jan. 2008, a updated therapeutic hypothermia protocol
- Cooling phase:  $<4$  hours, goal:  $33^\circ\text{C}$ 
  - Arctic Sun Cooling System, InnerCool RTx Endovascular System (Phillips Healthcare, Andover, MA)
- Give vecuronium 0.05  $\text{mg}/\text{kg}$  Q2HPRN for TOF 1/4-2/4 or visible movement, during the cooling and maintain phase

## GOAL OF THIS PAPER

- To compare the effect of intravenous continuous infusion versus intermittent bolus doses of vecuronium in therapeutic hypothermia after sudden cardiac arrest (SCA).

## STUDY DESIGN AND PATIENT SELECTION

- Retrospective, single-center (Memorial Hermann-Texas Medical Center, Houston)
- Patient  $\geq 18$  y/o who were treated therapeutic hypothermia after SCA
- Exclusion: no documented TOF measurement, no documented administration of vecuronium, died within 12 hours of initiation of the hypothermia protocol

## PATIENT COHORTS

- Vecuronium continuous-infusion group
  - During Jan 1, 2004 to Dec 31, 2007
  - Rate: 0.8  $\mu\text{g/kg/min}$
  - Goal TOF response 1/4 to 2/4 twitches
  - If TOF 0/4 twitches: stop the infusion; if  $> 0/4$ , resumed the infusion at half rate
  - Check TOF Q1H; if consistent for 3-4 hours, check Q2H
- Vecuronium bolus group
  - During Jan 1, 2008 to Sep 30, 2009
  - Dose: 0.05 mg/kg Q1HPRN if any shivering in the ED and CATH room
  - Dose: 0.05 mg/kg Q2HPRN for TOF 1/4 to 2/4 or visible movement in ICU
  - Check TOF Q2H

## STUDY OUTCOMES

- Primary outcomes
  - Time to achieve goal TOF response
  - The percentage of time with goal TOF response
- Secondary outcomes
  - Total daily dose of vecuronium
  - Vecuronium dose needed to achieve goal TOF response
  - Percentage of TOF measurements above or below goal
  - Time to return of spontaneous respirations
  - Time to extubation

## STATISTICAL ANALYSIS

- $\chi^2$  test (卡方檢定): to compare categoric data (自變數、依變數均屬類別變數時, 運用  $\chi^2$ -test 來檢驗其差異顯著性)
- Student T test to compare continuous data in 2 normal distribution groups (用來檢定兩個標準差未知之常態分配的平均值是否相等)
- Mann-Whitney U test: to compare continuous data in 2 non-normal distribution groups (為常用來替代 t 檢定之無母數統計法, 用於非常態的分布, 或樣本數不大, 或有違 t 檢定的假設時)
- P value  $< 0.05$ : statistically significant difference

## RESULTS

- 269 patient was reviewed, 146 were excluded in the continuous infusion group and bolus group:
  - 20+41: no TOF measurement
  - 16+49: no dose of vecuronium documented
  - 0+20: died less than 12 hours
- Total 123 patients were included
  - 80: continuous-infusion group
  - 43: intermittent-bolus group

Table 1. Baseline Demographic and Clinical Characteristics of the 123 Patients Who Received Vecuronium by Continuous Infusion or Intermittent Boluses

Characteristics	Continuous-Infusion Group (n=80)	Bolus Group (n=43)	p Value
Mean $\pm$ SD			
Age (yrs)	57.8 $\pm$ 16.4	57.3 $\pm$ 16.3	0.89
Weight (kg)	90 $\pm$ 25	84 $\pm$ 18	0.13
Body mass index	29.9 $\pm$ 8.1	28.9 $\pm$ 7.2	0.58
Time until hypothermia initiation (hrs)	8.7 $\pm$ 4.5	7.4 $\pm$ 5.5	0.16
No. (%) of Patients			
Male	52 (65)	15 (35)	0.85
Race-ethnicity			0.31
Caucasian	26 (33)	18 (42)	
African-American	40 (50)	14 (33)	
Hispanic	11 (14)	9 (21)	
Other	3 (4)	2 (5)	
Underlying arrhythmia			<0.0001
Ventricular fibrillation or tachycardia	73 (91)	25 (58)	
Pulseless electrical activity	5 (6)	3 (7)	
Asystole	2 (3)	15 (35)	
Liver dysfunction	2 (3)	1 (2)	0.58
Renal dysfunction	18 (23)	10 (23)	0.89

- Liver insufficiency: T-bil >2 mg/dL; AST and ALT >400 U/L
- Renal insufficiency: increased Creatinine  $\geq$ 0.3 mg/dL or U/O <0.5 mL/kg/hr >6 hr

Table 2. Primary Outcomes

Outcome	Continuous-Infusion Group (n=80)	Bolus Group (n=43)	p Value
Time to achieve goal TOF response (hrs)	11.3 $\pm$ 11.6	5.9 $\pm$ 8.5	0.038
Percentage of time TOF response was maintained at goal	40.3 $\pm$ 28.2	35.4 $\pm$ 25.1	0.34

Data are mean  $\pm$  SD.  
TOF = train-of-four.

Table 3. Secondary Outcomes

Outcome	Continuous-Infusion Group (n=80)	Bolus Group (n=43)	p Value
Mean $\pm$ SD			
Length of stay (days)	11.6 $\pm$ 13	9.2 $\pm$ 6	0.16
Total daily dose of vecuronium (mg)	76.9 $\pm$ 40	51.7 $\pm$ 40	0.002
No. (%) of Measurements			
TOF measurements			
Above goal (underparalysis)	207/622 (33)	248/530 (46)	<0.0001
Below goal (overparalysis)	182/622 (29)	66/530 (12)	<0.0001
Median (IQR)			
Vecuronium dose to achieve goal TOF response (mg)	97.3 (75.9–112.6)	28 (16.3–40.8)	0.0001
Duration of hypothermia (hrs)	28 (26.8–30)	29 (27–30)	0.18
Time to return of spontaneous respirations (hrs)	6 (1.3–14)	11 (4–22.8)	0.0175
Time to extubation (hrs)	29.5 (15–58)	89.5 (54–130)	<0.0001

TOF = train-of-four; IQR = interquartile range.

- In bolus group: less daily dose, more over paralysis, less dose to achieve goal TOF response, more time to return spontaneous resp, more time to extubation

## WAS THE TIME TO RETURN TO SPONTANEOUS RESPIRATION AND EXTUBATION REALLY LONGER IN BOLUS GROUP?

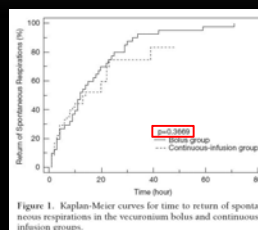


Figure 1. Kaplan-Meier curves for time to return of spontaneous respirations in the vecuronium bolus and continuous-infusion groups.

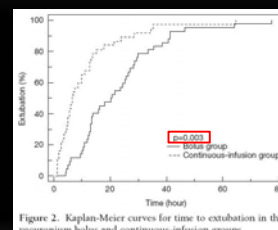


Figure 2. Kaplan-Meier curves for time to extubation in the vecuronium bolus and continuous-infusion groups.

- There was no difference in the time to return of spontaneous respiration in 2 groups!
- BUT! The time to extubation was really longer in bolus group!

## WHY WAS THE TIME TO EXTUBATION LONGER IN THE BOLUS GROUP?

Table 4. Time to Extubation by Logistic Regression Analysis

Variable	Coefficient	Standard Error of the Mean	95% Confidence Interval	p Value
Age	-0.035	0.015	0.936–0.996	0.027
Renal dysfunction	-2.27	1.064	0.012–0.829	0.033
Constant	1.41			

Age and renal function affected the extubation time!

## DISCUSSION

- 12 patients died within 12 hours of hypothermia:
  - May be due to the expansion of hypothermia protocol to asystolic >15 min
- Equal paralysis effect in 2 groups
- More underparalysis in continuous infusion group
  - May result in quicker time to return of spontaneous respiration and extubation
- Decreased metabolism was noted in hypothermic patients
  - Patient age and renal function were related to time to extubation
- This study did not evaluate the pneumonia (VAP or HAP) and APACHE II score

## LIMITATIONS

- A retrospective review
- Inconsistent documentation of TOF measurements and vecuronium doses
  - Therefore, many patients were excluded from the study
- The hospital- or ventilator-acquired pneumonia, underlying pulmonary disease and acuity of illness could also affect the time to return spontaneous respirations.
- Inability to control the quality of TOF documentation
- No data for length of stay (LOS) in ICU and in hospital

## CONCLUSION

- No guidelines for the usage of NM blocking agents
- Intermittent bolus of vecuronium would result in:
  - Faster to goal TOF response
  - Less dose to achieve goal TOF response
  - Less daily dose
  - More overparalysis
  - Slower return of spontaneous respiration (median) and extubation (but age and renal function were more effective)

## THANKS

## QUESTION 1: DR. LO

- 這篇 paper 的 Table 3
- 其中 TOF measurements, continuous 組共有 622 次, bolus 是 1530 次, 但是 continuous 組的病人其實比 bolus 多呢 (80 vs. 43)
- 內文有提到 continuous 組的測量是開始 load 上後每小時測到平衡, 若變成 0/4 就減半 dose 再每小時測量, 但意思似乎不是固定每小時量, 而是發現 abnormal 才去啟動監測; 相對於 continuous 組, bolus 組在 ICU 裡就固定兩小時測一次, 兩者在發動 measurement 這個動作上似乎存在有 bias, 而不能單單用  $p < 0.001$  就說是有意義。

## QUESTION 2: DR. CHOU

- study 中放了很多 parameter 例如 age, liver function, renal insufficiency
- 但似乎沒有針對這些 parameter 對實驗結果造成的影響誤差多做著墨
- 只有在 result 的最後一行提到 "intermittent bolus dosing was dependent on age and renal function"
- 我的問題是: 如果真要把這些 parameter 加進去去看跟研究結果的 correlation~ 該如何設計或是用何種統計檢定方式會比較恰當?

## QUESTION 3: DR. YU

- 這篇 paper 是在討論 Continuous 或 Intermittent 注射 Vecuronium。
- 不知道文中是否有提及 Vecuronium 是從 CVC 或是從 peripheral IV 投藥?
- 又, 不同的投藥途徑是否有可能對結果產生不同的影響呢?
- 謝謝!

#### QUESTION 4: DR. HSU

- 1. 達到TOF = 0 之後會有何種side effect? 若有, 那用bolus會不會造成此種side effect機會增加
- 2. 此篇paper結論看起來似乎持續infusion那組並無什麼優點? 是否表示可改為用bolus即可?