神經麻醉用藥 及

開顱手術之輸液治療

陳冠宏醫師

神經麻醉用藥的理想特性

- 維持CMR(腦代謝率)和CBF(腦血流)的耦合
- 不會增加CBV(腦血容量)或ICP(腦壓)
- 維持腦血管自動調節
- 具神經保護作用
- 具抗癲癇作用
- 具穩定血流動力學
- 快速恢復

Barbiturate (Citosol)

- ↓CMR & CBF in dose-dependent
  - Decreases oxygen demand
    - ↓Rate of ATP consumption
    - CMR suppression-induced cerebral vasoconstriction
  - Isoelectric EEG (CMR & CBF ↓50%)Anesthesiology 1974;41:231-236,/J. Clin. Invest.1962;41:1664-71/Acta Anaesthesiol. Scand. 1984;28:478-81
    - High dose (10-55 mg/kg)
    - IV infusion: 4-6 mg/kg/hr

Barbiturate (Citosol)

- Preserved CO2 responsiveness & autoregulation Clin. Neurosurg. 1969;1:378-418/J. Neurosurg. 1981;54:615-619
- Robin Hood or Reverse Steal Phenomenon
  - Cerebral vasoconstriction only in normal areas → Blood redistribution to ischemic vasodilated areas

Barbiturate (Citosol)

- (+) CSF absorption → ↓ICP
- Excitatory amino acid receptor blockade
- Stabilize membranes → Decrease seizure activity → Anticonvulsant effect
- (-) Na channels &↓Intracellular Ca influx
- Free radical scavenging

Propofol

- ↓CMR, CBF, ICP
  - Decreases oxygen demand
    - ↓Rate of ATP consumption
    - CMR suppression-induced cerebral vasoconstriction
  - Direct cerebral vasoconstriction
  - Bolus + Infusion: ↓CMR 36%, CBF 51%, ICP 30%
    Anaesthesist 1987;36:60-65/Anaesthesia 1988;43[Suppl]:37–41/Anesthesiology 1995;82:393-403
- Preserved CO2 responsiveness & autoregulation Anesthesiology 1992;77:453-56, 1995;83:88-95/J. Neurosurg Anessthesiol 1992;4:298/A&A 1993;76:S163

Dexmedetomidine (Precedex)

- α2 agonist
- 作用部位
  - α2-receptor（特別集中於大腦第4腦室底上角藍斑核神經元上）受刺激後，產生負回饋抑制的效用
- 作用部位
  - Brain (Locus coeruleus藍斑核)
  - Spinal cord 脊髓
  - 交感神經

Dexmedetomidine (Precedex)

- 中樞神經之作用
  - Sedation鎮靜
  - Anxiolysis抗焦
  - Analgesia止痛
  - 降低腦代謝率
  - 降低腦血流
  - Neuroprotection
- 交感神經之作用
  - 降低交感神經活性
  - 降低心跳血壓

Precedex 200mcg/2ml注射劑量
(每瓶請稀釋成50mL：2ml Precedex + 48ml N/S)

初劑量　以 1.0 mcg/Kg 的劑量持續輸注十分鐘

初劑量輸注 (Loading Infusion)											
病患體重 (Kg)	40	45	50	55	60	65	70	75	80	85	90
以 1.0mcg/kg 的初劑量持續輸注十分鐘所需設定的流速 (ml/hr)											
持續輸注十分鐘所需設定初劑量之流速 (ml/hr)	60	67.5	75.0	82.5	90	97.5	105	112.5	120	127.5	135
所需輸注之總溶液量 (ml)	10	11.25	12.5	13.75	15	16.25	17.5	18.75	20	21.25	22.5

* Precedex® (2ml) 以氯化鈉溶液 (48ml) 稀釋為最終濃度 4mcg/ml

維持劑量　以 0.2~0.7 mcg/kg/hr 的劑量持續輸注

維持劑量輸注 (Maintenance Infusion)											
輸注流速 (ml/hr) / 維持劑量 (mcg/kg/hr)	病患體重 (Kg)										
	40	45	50	55	60	65	70	75	80	85	90
0.2	2.0	2.2	2.5	2.7	3.0	3.2	3.5	3.7	4.0	4.2	4.5
0.3	3.0	3.3	3.7	4.1	4.5	4.8	5.2	5.6	6.0	6.3	6.7
0.4	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0
0.5	5.0	5.6	6.2	6.8	7.5	8.1	8.7	9.3	10.0	10.6	11.2
0.6	6.0	6.7	7.5	8.2	9.0	9.7	10.5	11.2	12.0	12.7	13.5
0.7	7.0	7.8	8.7	9.6	10.5	11.3	12.2	13.1	14.0	14.8	15.7

開顱手術之輸液治療

- 開顱手術輸液給予考量

1. How: 如何給輸液量
2. What: 給什麼輸液
3. When: 什麼時候給血液製品

問題一

- 面對開顱手術的病患，要限制水分避免腦腫嗎？

Effect of Fluid Loading on the Brain

Craniotomy

大量

30 ml/kg Plasmalyte ←

→ <2 ml/kg Plasmalyte

限水

大腦皮質的血液灌流是減少

- Lower cerebral cortex perfusion
- Altered endothelial glycocalyx structure

血管內皮的glycocalyx結構是被破壞的，可能導致血腦屏障的不完整及後續的腦腫

Dostalova et al. J Neurosurg Anesthesiol 2018 ePub.

探討外傷性腦損傷後的神經學預後

Fluid Balance and Poor Neurologic Outcome in TBI

Variable	Chi-Square	P-Value
Admission GCS	29.17	<0.0001
Age	12.41	0.0004
MAP < 70 mmHg	8.21	0.0042
Lowest Quartile Fluid (-594 ml/96h)	7.95	0.0048
ICP >25 mmHg	4.03	0.0448
CPP <60 mmHg	1.10	0.2947

限水：
I/O負平衡

Lowest fluid quartile associated with higher rate of poor neurologic outcome (67% vs 54%)

Clifton et al. Crit Care Med 2002; 30:739 –745.

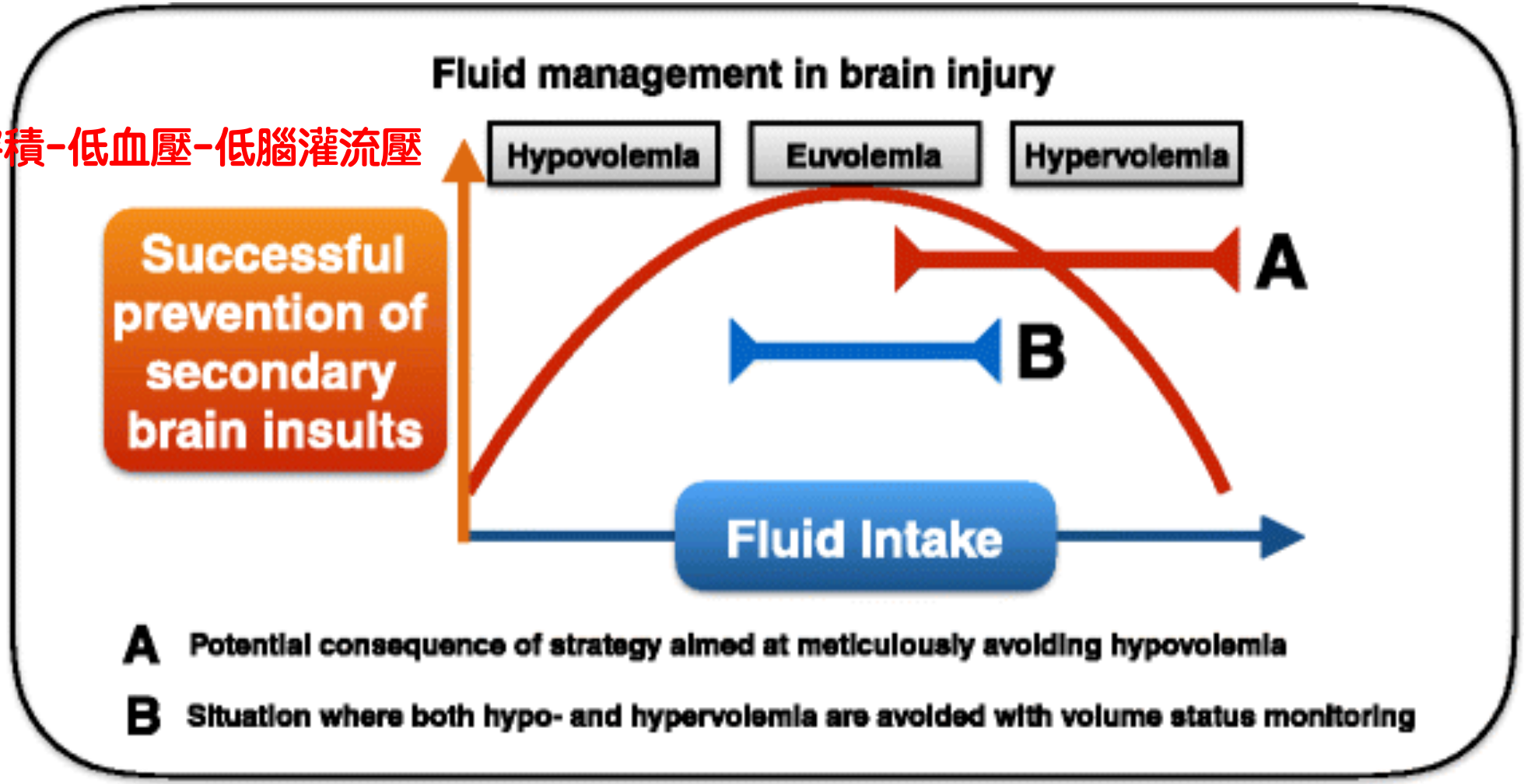
Fluid Balance and Outcome after TBI

"Our data support maintenance of euvolemia, fluid replacement with mannitol therapy and targeting a cerebral perfusion pressure of 70 mm Hg to avoid any occurrence of CPP < 60 mm Hg."

外傷性腦損傷，水分維持正常血容積，目標CPP 70 mmHg，避免CPP <60 mmHg

Clifton et al. Crit Care Med 2002; 30:739 –745

低血容積-低血壓-低腦灌流壓



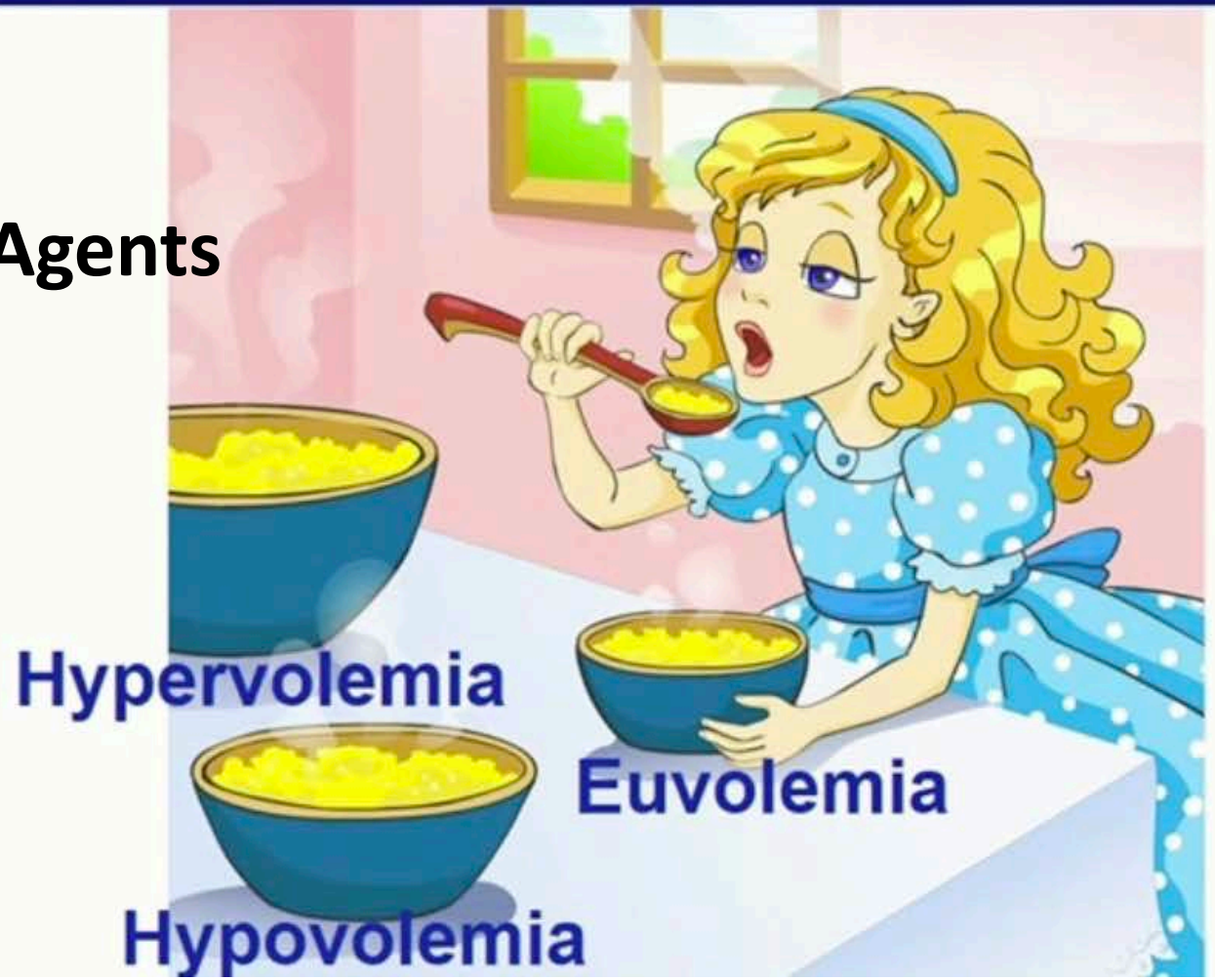
在一次腦損傷後，為了避免第二次的腦損傷，水分給予目標維持在正常的血容積

Relation between volume status, fluid intake and risk of secondary brain injury (SBI) in critically ill brain-injured patients

Crit Care. 2016; 20: 126.

Fluid Balance and Neurologic Injury

Inotropic Agents



運動

A-line CCO-Fluid responsiveness

- **1. ProAQT (Pulsion Medical Systems, 德國)**
- **2. FloTrac (Edwards Lifesciences, 美國)**
- 3. MostCare (VytechHealth, 義大利)
- 4. LiDCO rapid (LiDCO Ltd., 英國)

Goal Directed Fluid Therapy

Craniotomy for Supratentorial Tumor

早期補水

Low SVV Target ≥10%
N=40

VS

晚期補水

High SVV Target ≥ 18%
N=40

Low SVV ≥10% group:

Higher volume of colloid (869 vs 564 ml, p=0.0025)

Shorter ICU stay (1.4 vs 2.6 days, p=0.033)

Fewer postoperative neurologic events (17.5 vs 40%, p=0.047)

水分相對較多、但ICU時間相對短且較 少術後神經學病發症

Wu et al. BJA 2017:119(5): 934-942

問題二

- 面對開顱手術的病患，應該哪種輸液？

Choice of Fluid

Crystalloid

Colloid

Blood

Later ....

Balanced Crystalloids vs Saline

Balanced Crystalloid vs Normal Saline

Outcome	Non-Critically Ill Adults Adj OR (95%CI)	Critically Ill Adults Adj OR (95%CI)
Major adverse kidney event	**0.82 (0.70-0.95), p=0.01** 非重症患者	**0.90 (0.82-0.99), p=0.04** 重症患者
> Stage 2 AKI	0.91 (0.80-1.03), p=0.14	0.91 (0.82-1.01), p=0.09
In-hospital death <30 days	0.88 (0.66-1.16), p=0.36	0.90 (0.80-1.01), p=0.06

The NEW ENGLAND JOURNAL of MEDICINE

Semler et al. NEJM 2018;378(9):829-39; Self et al. NEJM 2018;378(9):819-28

Balanced Crystalloid vs Normal Saline

"Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline."

The NEW ENGLAND JOURNAL of MEDICINE

Self et al. NEJM 2018;378(9):819-28

Albumin

Albumin and the Brain

Disadvantages

↑ Cerebral colloid pressure and edema if extravasation occurs

Hypotonic stress*

Advantages

↑Blood oncotic pressure

↓Brain edema

Antioxidant

Baker et al. J Trauma 2008;64:348-57

Crystalloid vs Colloid in TBI

TBI
+/-
Hemorrhage

- 0.9% NS
- 3% NS
- 5% Albumin
- Whole blood

Albumin:
Higher PaO_2
Higher PbO_2

Baker et al. J Trauma 2008;64:348-57

Albumin vs Crystalloid Solutions

The NEW ENGLAND JOURNAL of MEDICINE

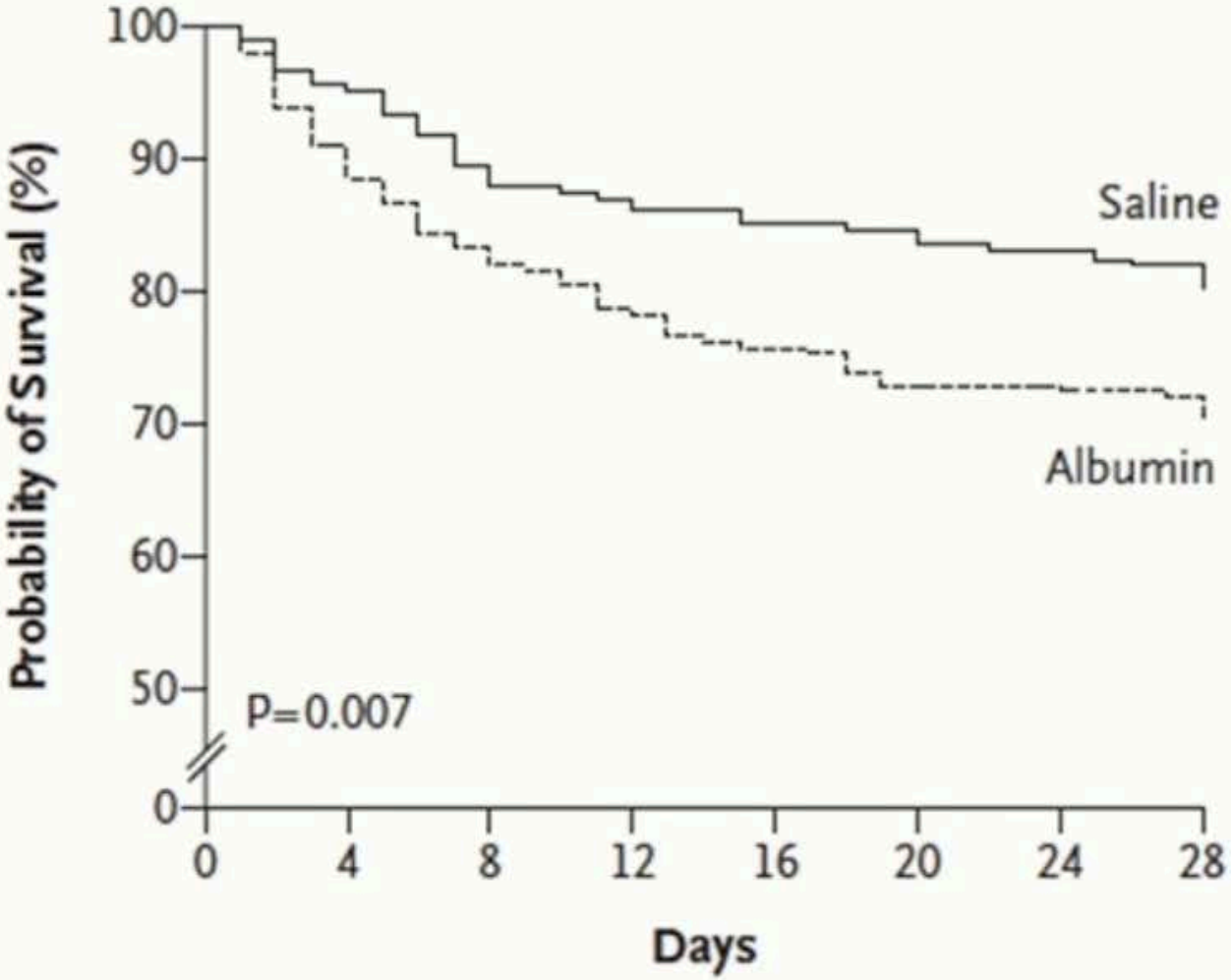
ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

In patients in the ICU, use of either 4% Albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days

SAFE Study Investigators. N Engl J Med 2004;350(22):2247-56

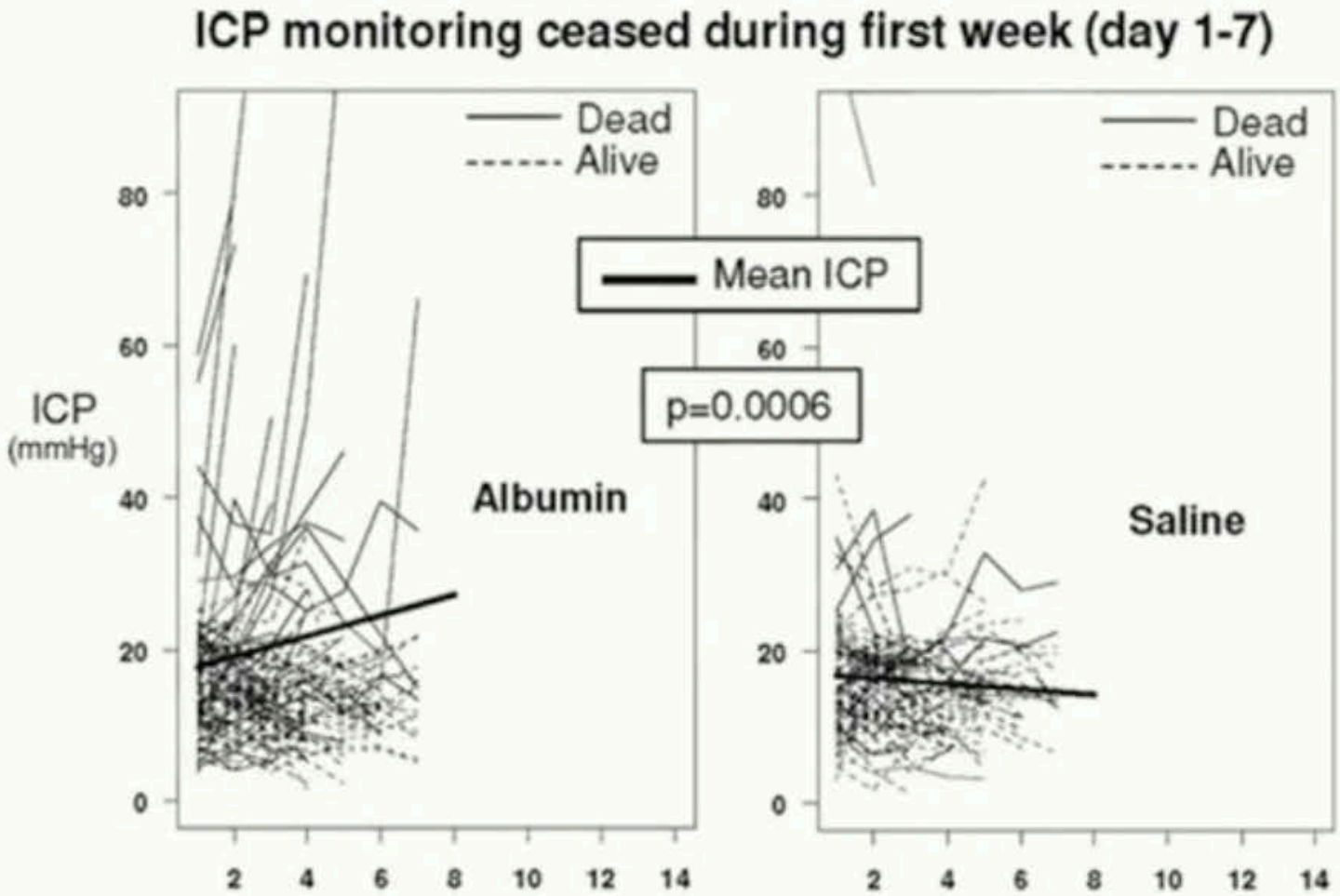
Albumin vs Crystalloid Solutions: TBI



- Subgroup analysis of TBI patients (n=460)
- Mortality higher in albumin group (33% vs 24%)
- Effect driven by severe TBI group (GCS 3-8) (42% vs 22%)

SAFE Study Investigators. N Engl J Med 2007;357:874-84

Albumin vs Crystalloid Solutions: TBI



Hypothesis

Extravasation of albumin increased cerebral interstitial osmotic pressure and ICP

Cooper et al. J Neurotrauma 2013;30:512-8

Synthetic Colloids

Synthetic Colloids vs Crystalloid: ICU

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

Ryan Zarychanski, MD, MSc
Ahmed M. Abou-Setta, MD, PhD
Alexis F. Turgeon, MD, MSc
Brett L. Houston, BSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Fergusson, PhD, MHA

Importance Hydroxyethyl starch is commonly used for volume resuscitat been associated with serious adverse events, including acute kidney injury . Clinical trials of hydroxyethyl starch are conflicting. Moreover, multiple trial investigator have been retracted because of scientific misconduct.

Objectives To evaluate the association of hydroxyethyl starch use wit and acute kidney injury.

Data Sources Randomized controlled trials from MEDLINE, EMBASE, CENTF Health, HealthStar, Scopus, Web of Science, the International Clinical Tria Platform (inception to October 2012), reference lists of relevant articles

JAMA®
The Journal of the American Medical Association

Use of HES associated with increased risk of mortality and AKI*

Zarychanski et al. JAMA 2013;306(7): 678-88

Crystalloid vs Colloid: Brain Relaxation

Craniotomy for Supratentorial brain tumor

GDT-RL	VS	GDT-HES
N=20		N=20

Similar brain relaxation scores and cerebral metabolism (SjvO2)

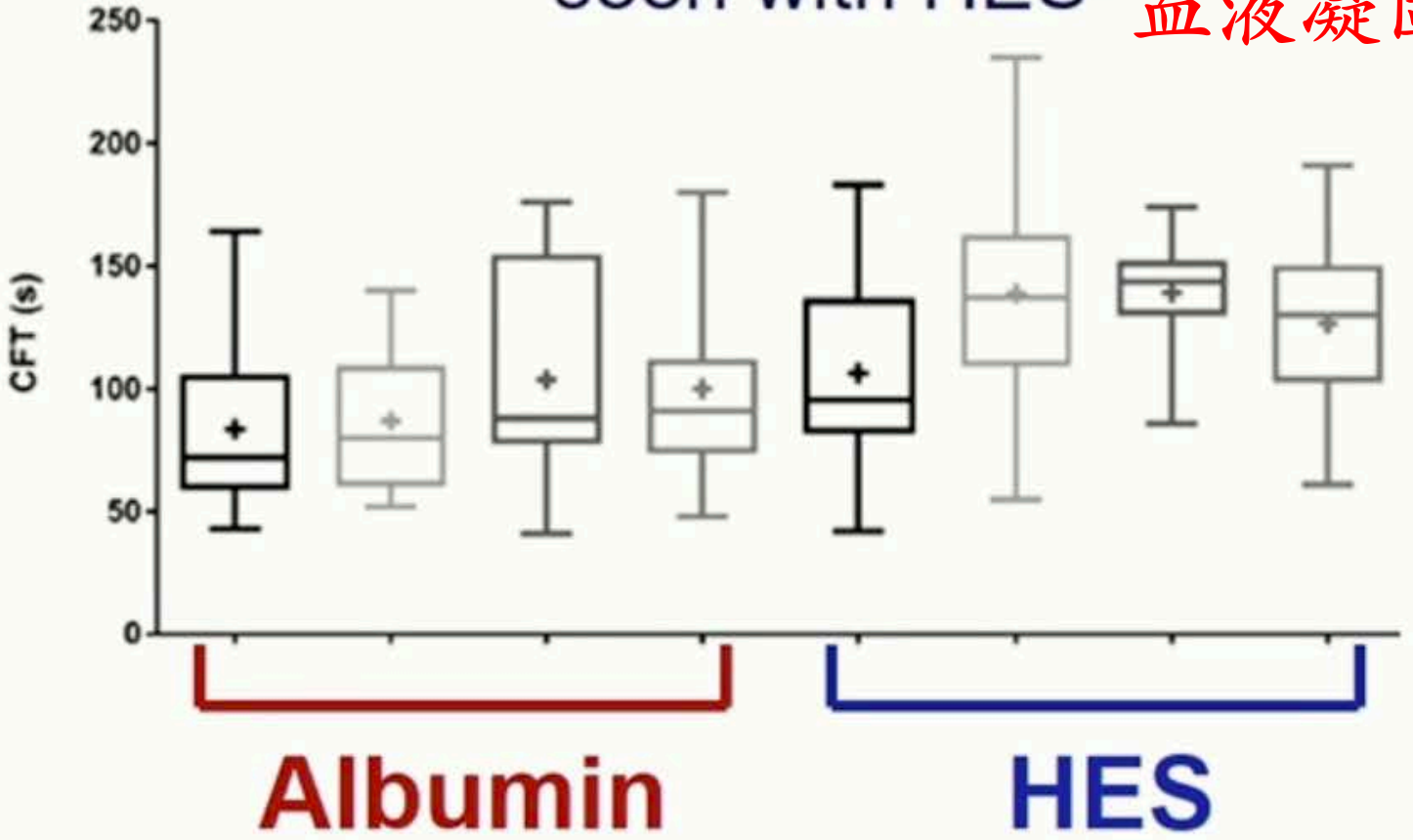
兩者的腦鬆弛度和腦代謝都沒有差異

Xia et al. J Neurosurg Anes 2014;26:320-327

Coagulopathy and Synthetic Colloids

Earlier and more profound alterations in thromboelastography seen with HES

血液凝固動態變化測驗

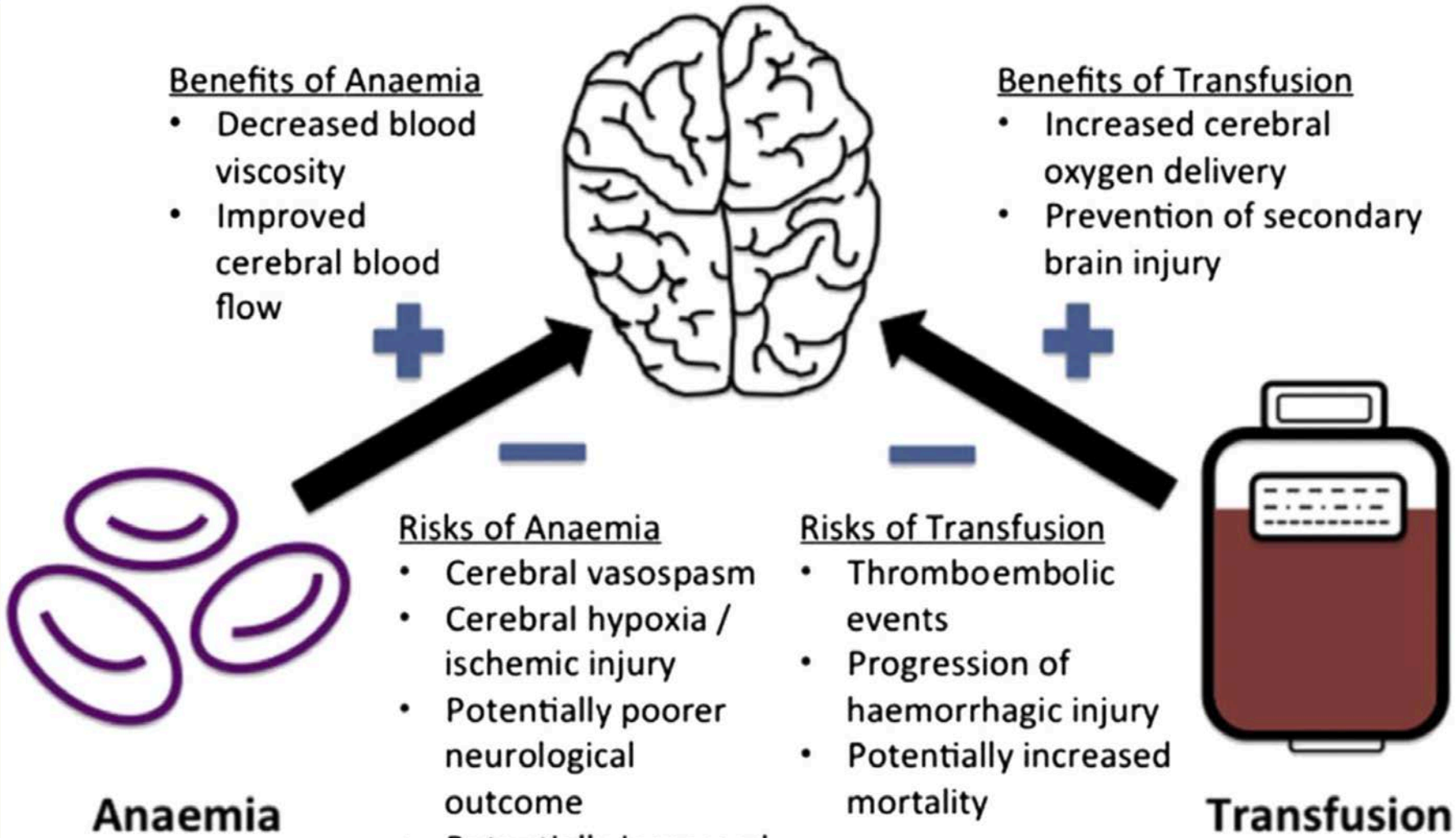


Li et al. Periop Med 2015;4:9

問題三

- 面對開顱手術的病患，什麼時候該輸血？

Risks/Benefits of Transfusion



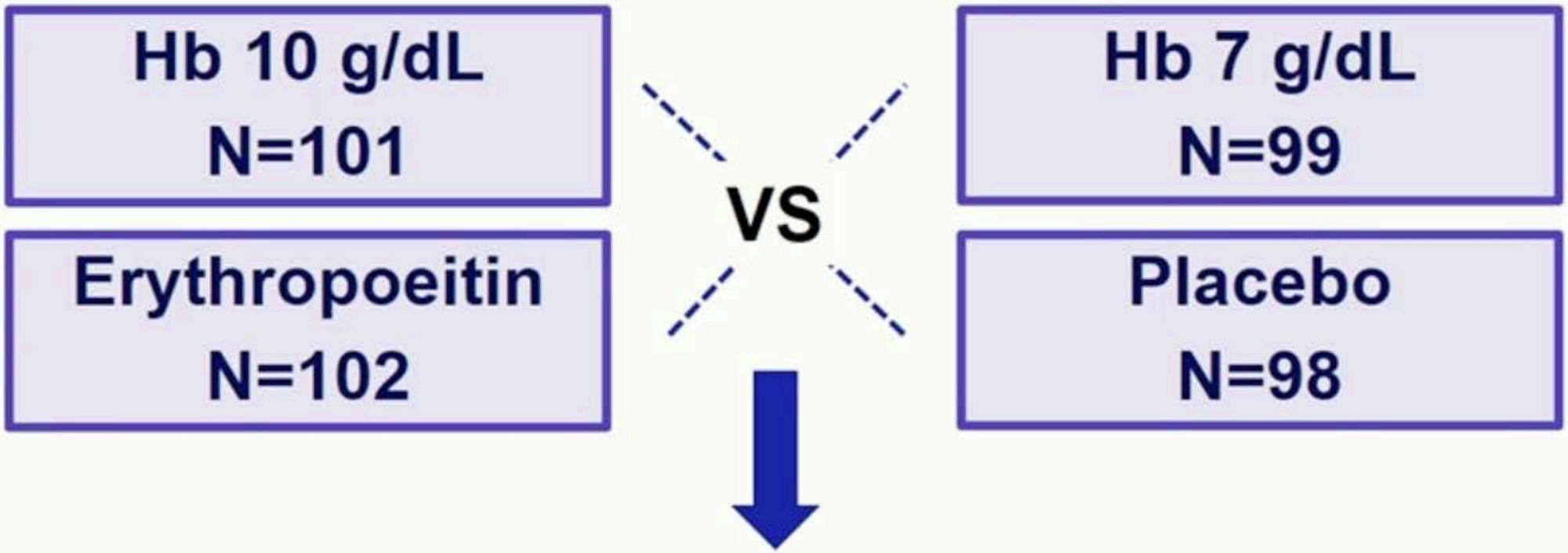
Kisilevsky et al. BJA 2018, 120(5):988-998

Anemia → Poor Outcomes?

- Cognitive dysfunction apparent at Hb 5-6 g/dL
- Duration of anemia (Hb<9 g/dL) associated with poorer outcomes in severe TBI in several studies

Kisilevsky et al. BJA 2018;120(5):988-9989

EPO + Transfusion Threshold in TBI



Glasgow Outcome Scale 6 months post-injury

Robertson et al. JAMA 2014;312:36-47

EPO +Transfusion Threshold in TBI

Hb Target	Hb after enrollment (range)	Favorable GOS	Adjusted OR (95% CI) favorable GOS	Thrombo-embolic events
7 g/dL	9.7-10.8 g/dL	42.5%	Ref	8.1%
10 g/dL	11.4-11.7 g/dL	33%	0.75 (0.36-1.55) p=0.43	21.8%

Secondary analysis: 2.3-fold increase in hemorrhagic transformation with higher transfusion threshold

Robertson et al. JAMA;312:36-47; Vendantam et al. J Neurosurg 2016;125:1229-34

Take Home Message

- 輸液：
  - 過多過少都不行
  - 正常的血容積：目標導向輸液治療
- 平衡性輸液是首選輸液
- 人工代用血漿會造成血液凝集障礙、腎臟損傷等
- 白蛋白可能會造成腦壓增高
- 血紅素約略維持在9-10 g/dL
  - 個別化分析輸血利與弊

End.....