

高张盐水治疗高颅压

——过去，现在和未来

北京天坛医院神经病学中心

神经重症医学科

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HS的药理学



北京天坛医院

Beijing Tiantan Hospital

渗透梯度

Sodium Chloride Concentration (%)	Osmolarity (mOsm/L)	Sodium Concentration (mEq/L)
0.9	308	154
1.7	582	291
3.0	1026	513
7.5	2566	1283
10.0	3424	1712
23.4	8008	4004

For comparison, the osmolarity of 20% mannitol is 1098 mOsm/L.

血浆渗透压正常值为: **280-295 mOsm/l**

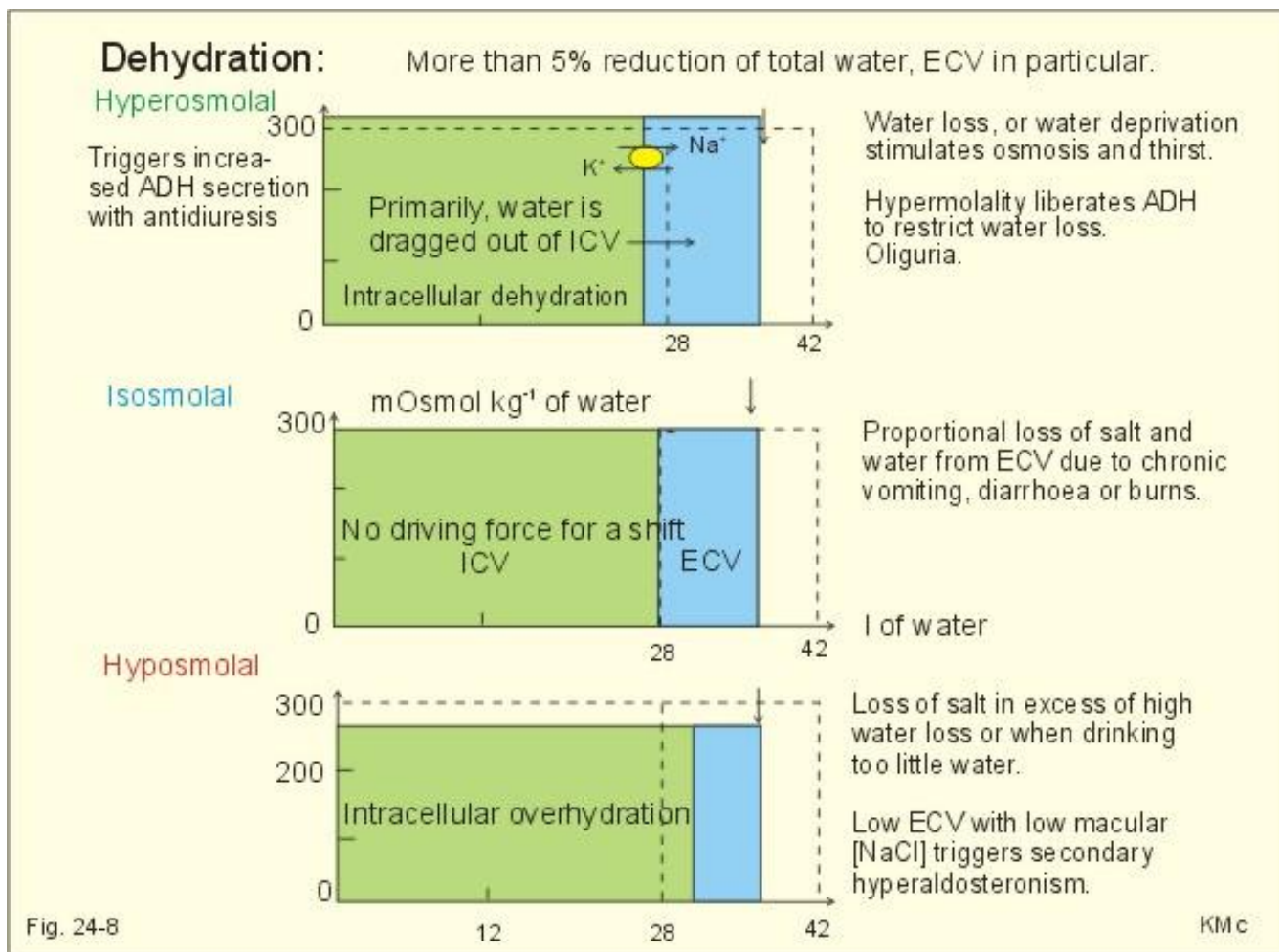


反射系数

- 维持渗透梯度取决于溶质被血脑屏障排斥的程度
- 反射系数 [0 (表示完全通透性) -1 (表示完全不透性)]
- 钠的反射系数接近1.0, 甘露醇反射系数为0.9
- 理论上讲, HS更容易维持渗透压梯度, 不易发生颅内压反弹



水从ICV到ECV



过去……



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1919年霍普金斯医学院

PRESSURE CHANGES IN THE CEREBRO-SPINAL FLUID FOLLOWING INTRAVENOUS INJECTION OF SOLU- TIONS OF VARIOUS CONCENTRATIONS

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Ringer's液-100ml

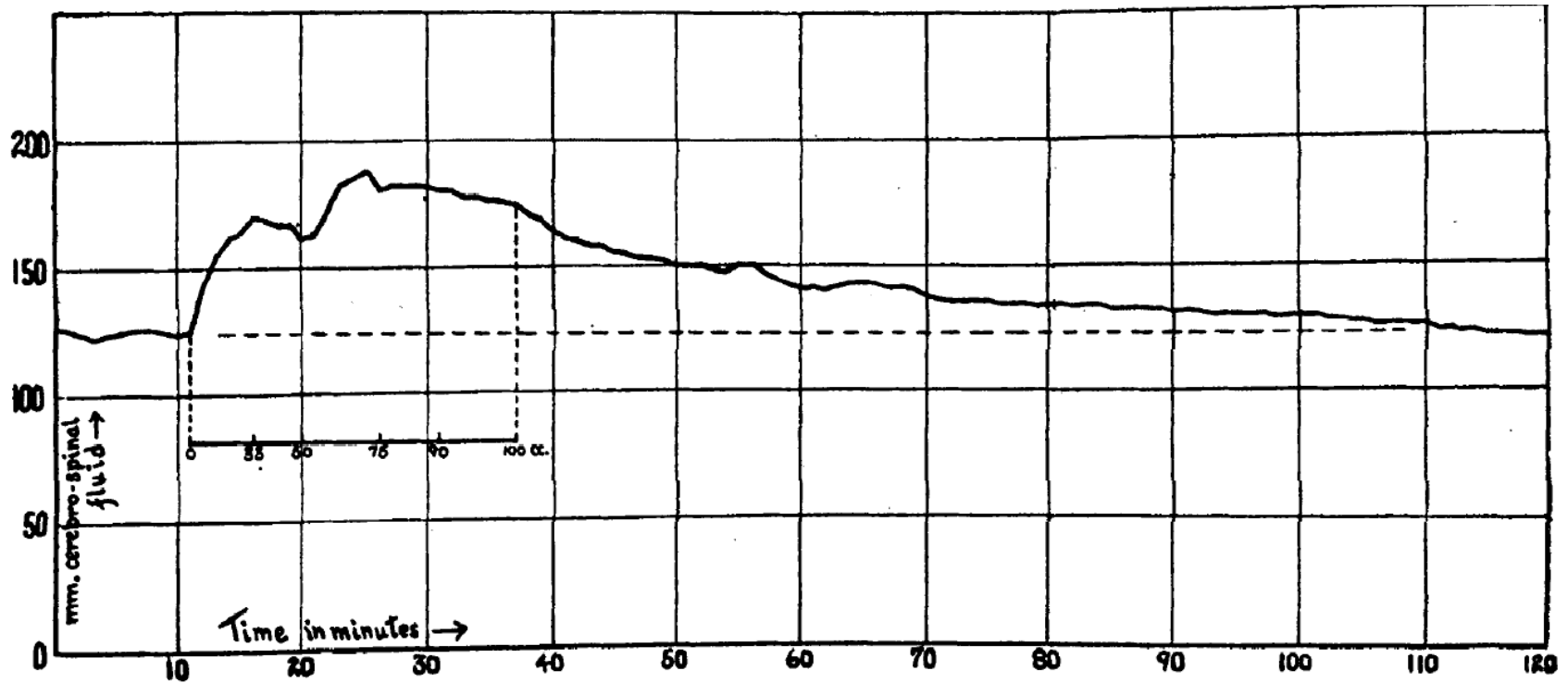


Fig. 3. Cat no. 1543. Pressure cerebro-spinal fluid with intravenous injection 100 cc. of Ringer's solution.



低张溶液-20ml蒸馏水

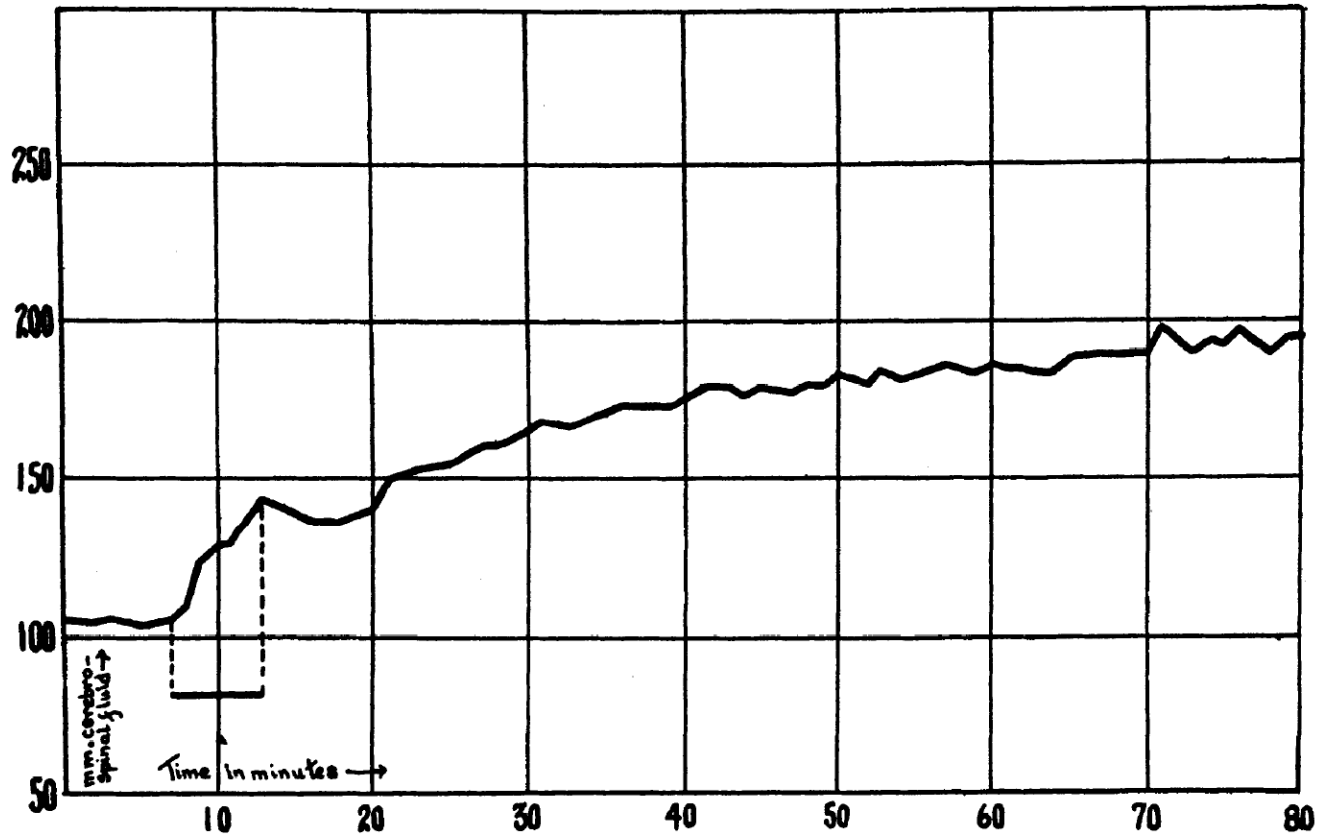


Fig. 4. Cat no. 1303. Pressure cerebro-spinal fluid with intravenous injection of 20 cc. sterile distilled water.



高张溶液-30%盐水12ml

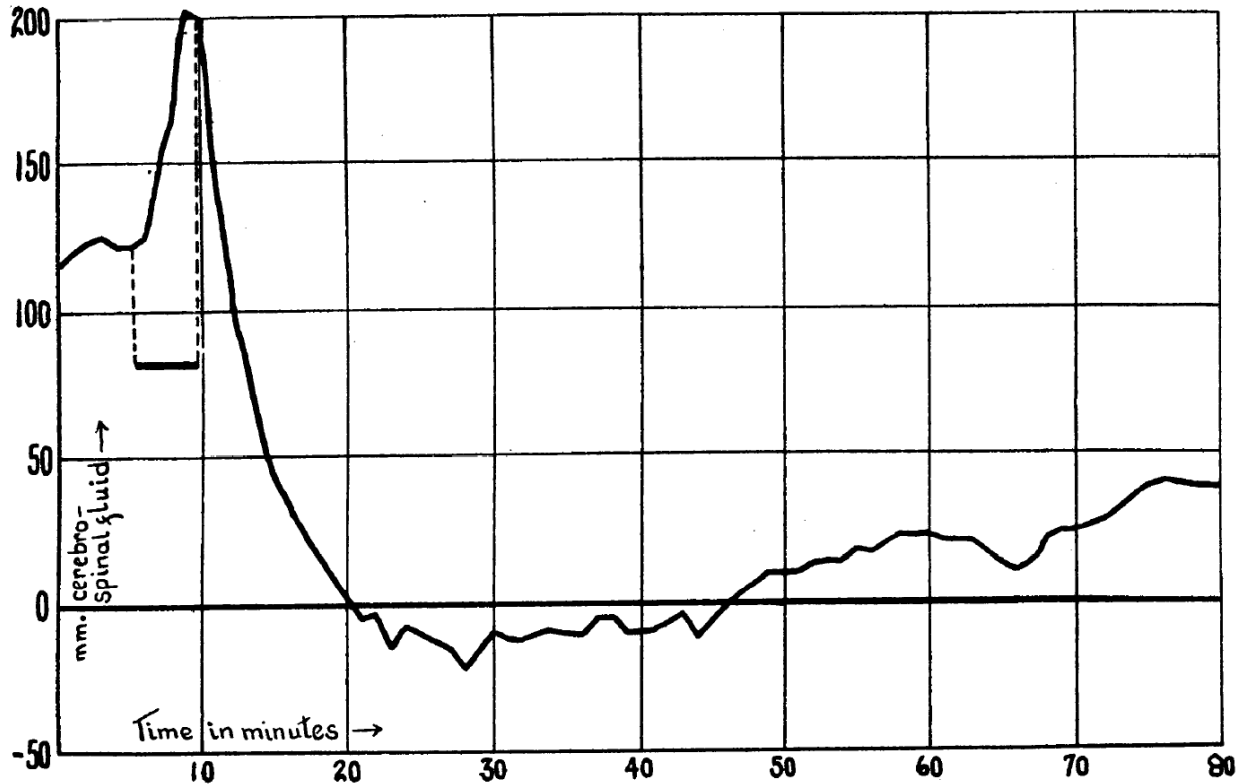
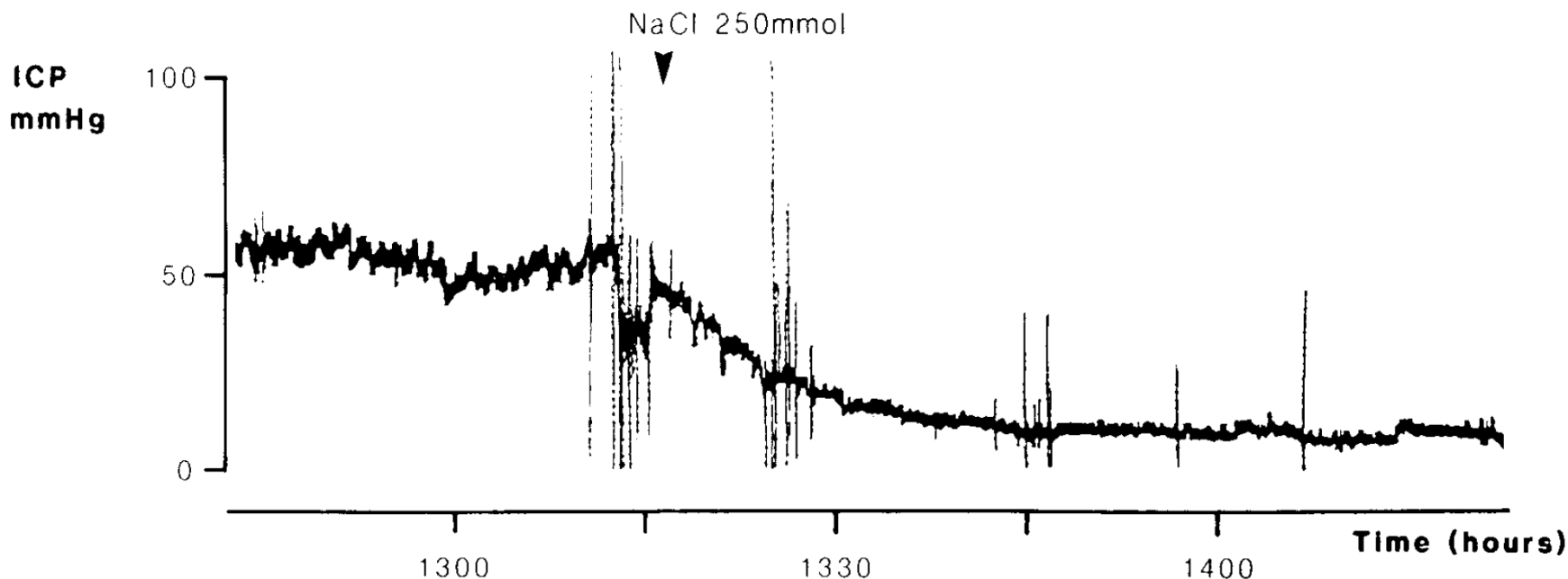


Fig. 6. Cat no. 1271. Pressure cerebro-spinal fluid with intravenous injection of 12 cc. 30 per cent sodium chloride.



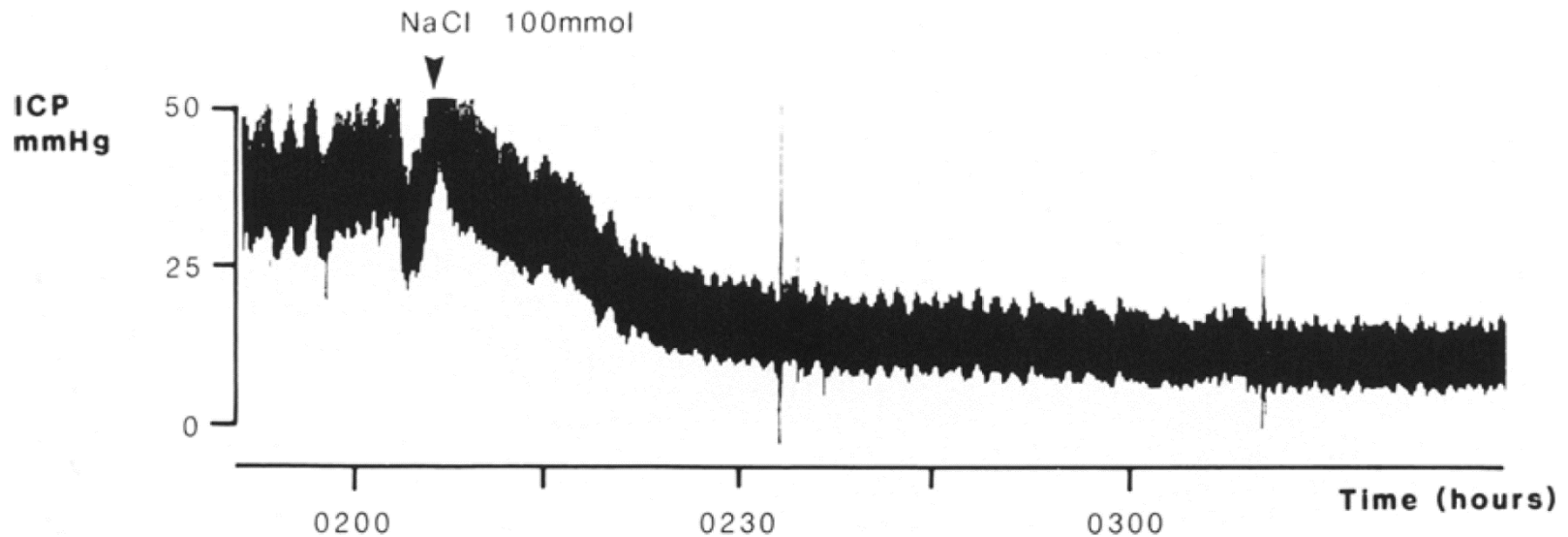
七十年后临床病例报道-CASE1

TBI后36h, ICP 40mmHg, MAP 83-85mmHg, 20g Mannitol q2h; 48h, 液体副平衡 2200ml, 少尿, BP 110/85mmHg, CVP 2mmHg, Cr 0.28mmol/l, 渗透压305mOsm/kg, 血钠131mmol/l; 过度通气pCO₂ 25mmHg, 予100ml Mannitol, ICP 由45降低到 32mmHg; 20min后ICP 53mmHg, 予30% HS 250 mmol, ICP 10mmHg; 1h后 BP 140/80 mmHg, CVP 6mmHg, 血钠137mmol/l; 24h后ICP 8-12mmHg, 尿量增加

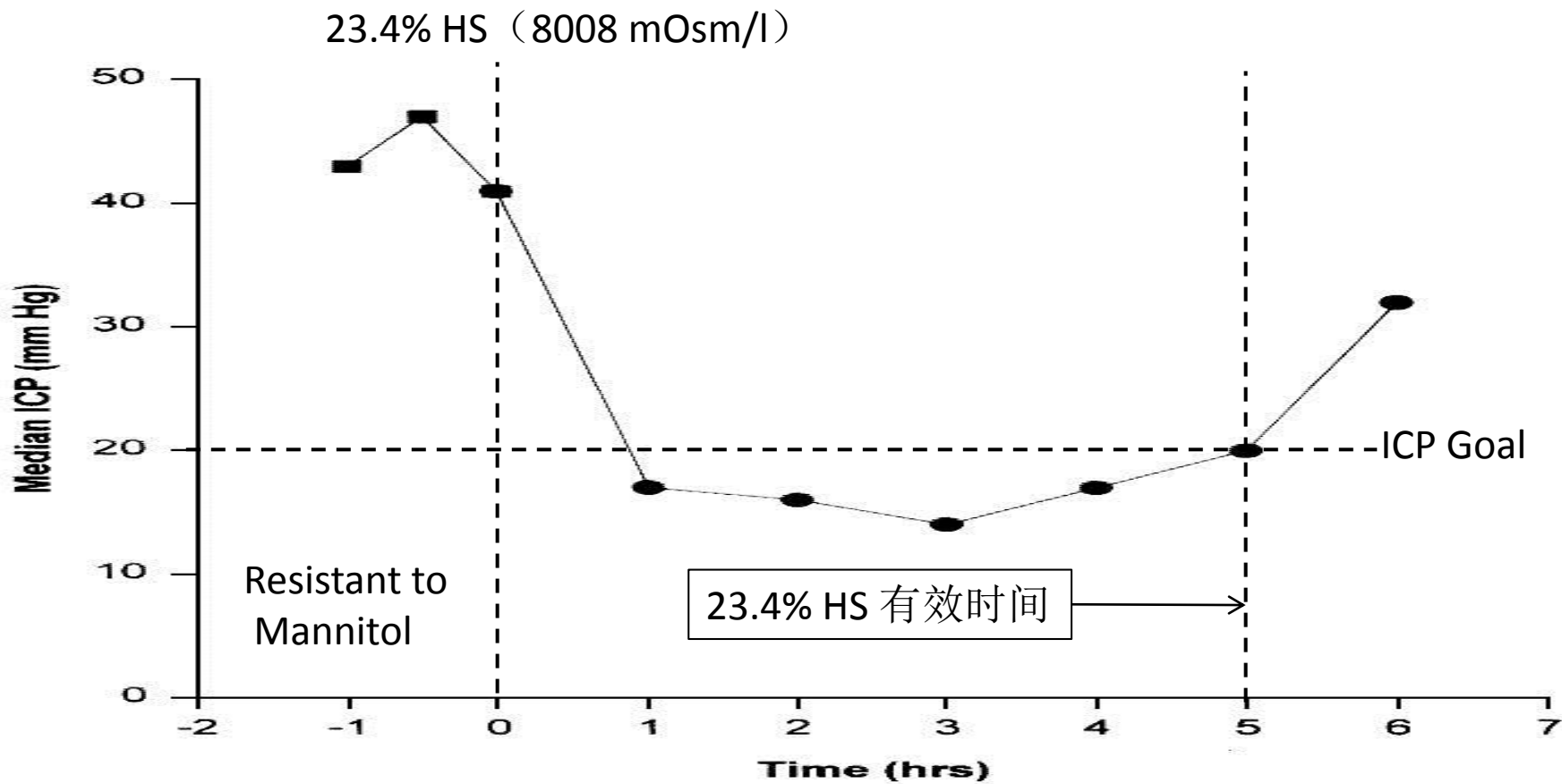


七十年后临床病例报道-CASE2

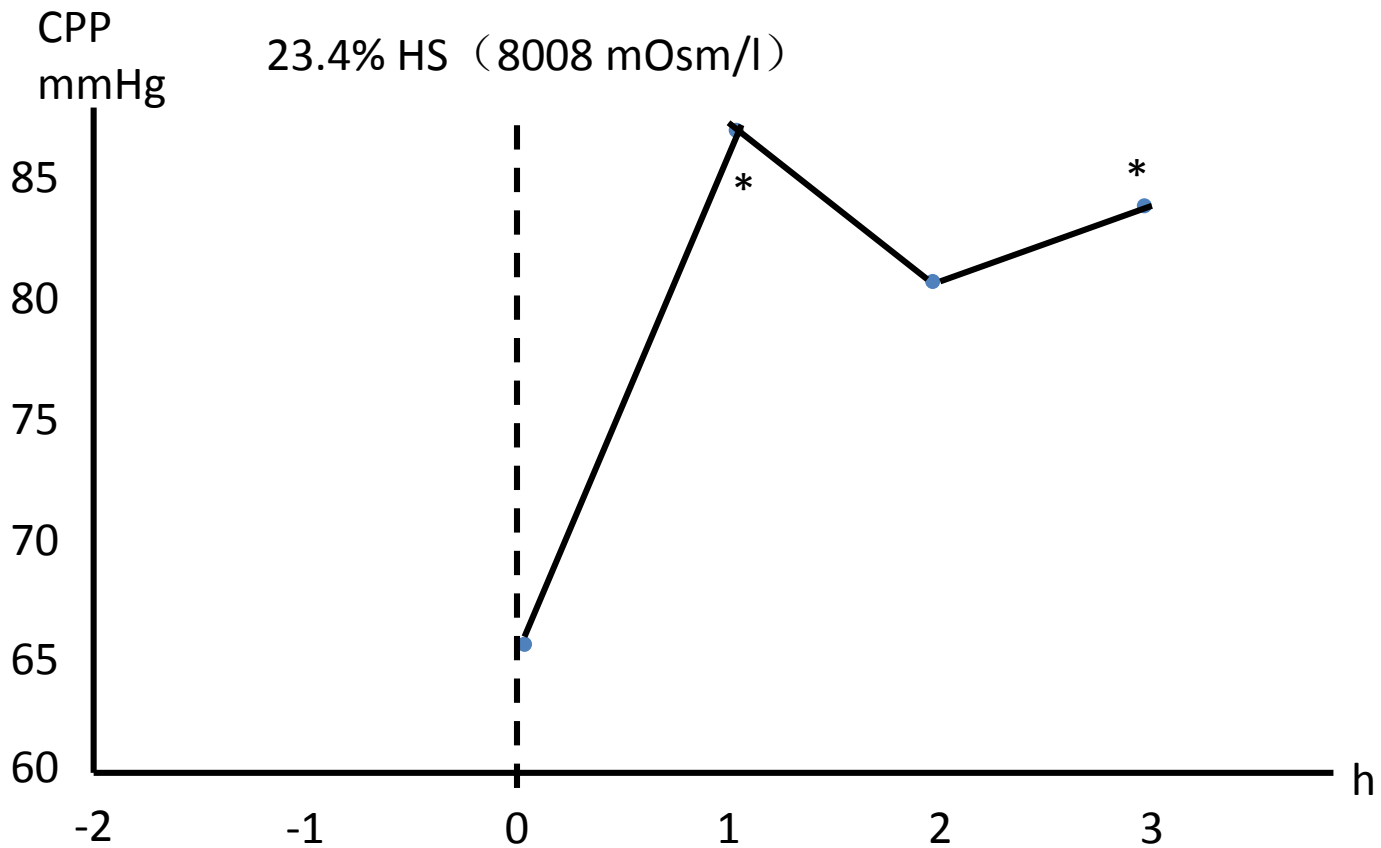
17岁TBI, ICP 25-30mmHg, 200ml 20%Mannitol 2次, ICP和尿量没有变化, BP 125/90mmHg,CVP 0, 血钠139mmol/l, Cr 0.21mmol/l。30% HS 100mmol,ICP 10mmHg持续12h。CVP升高到4mmHg, 肾功能恢复



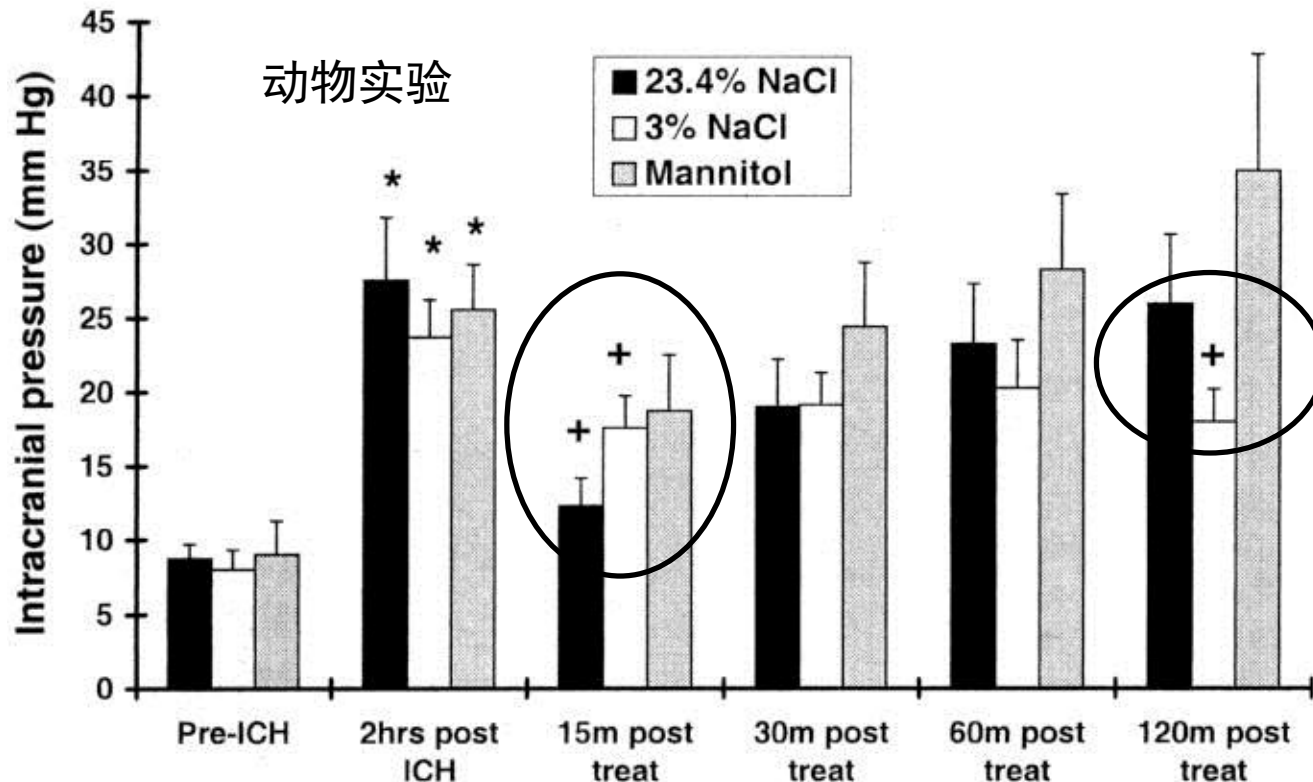
十年后8个回顾性病例报道



十年后8个回顾性病例报道

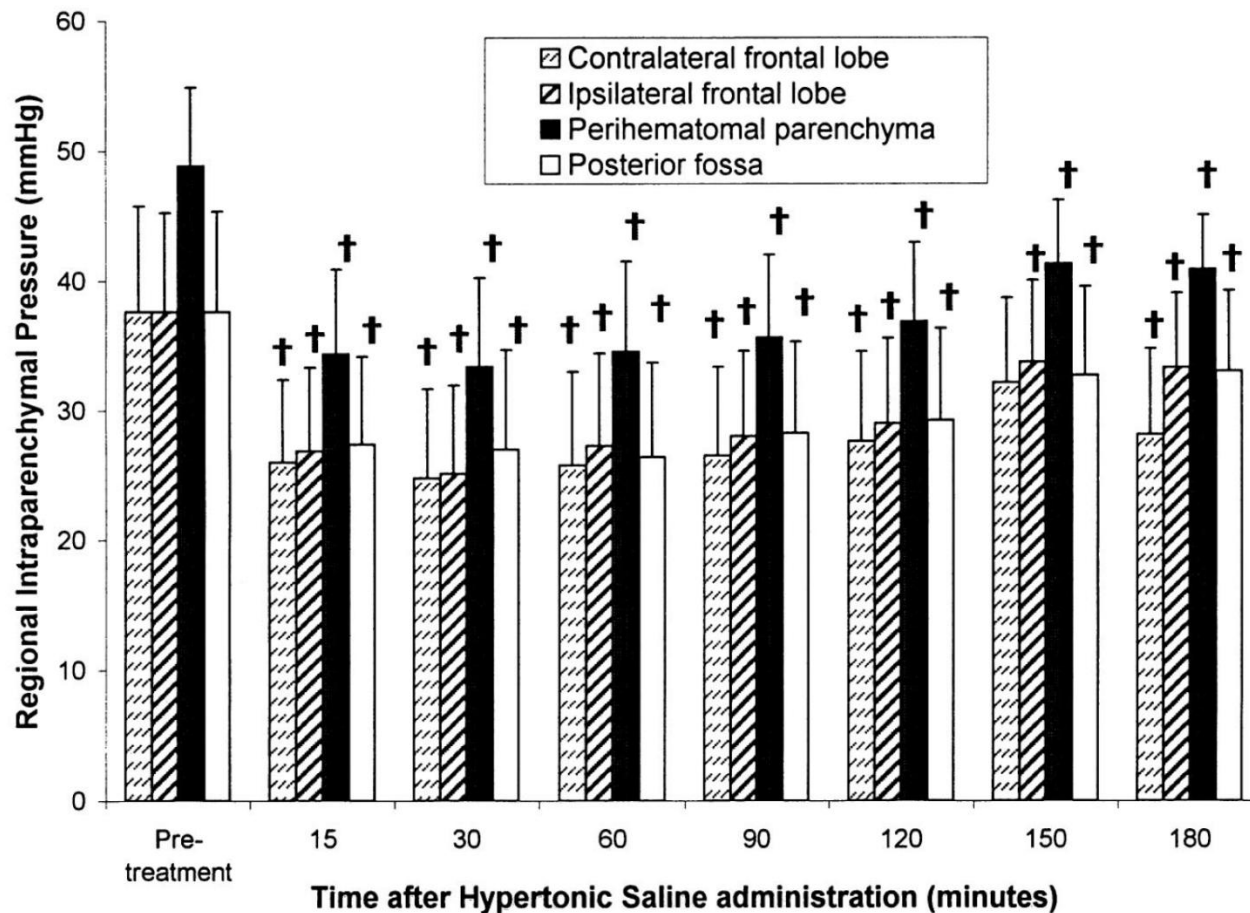


第二年不同制剂对ICP的作用



+, value significantly lower than the pretreatment value

2002年单剂23.4% HS 对不同部位ICP的作用



现在(近十年).....

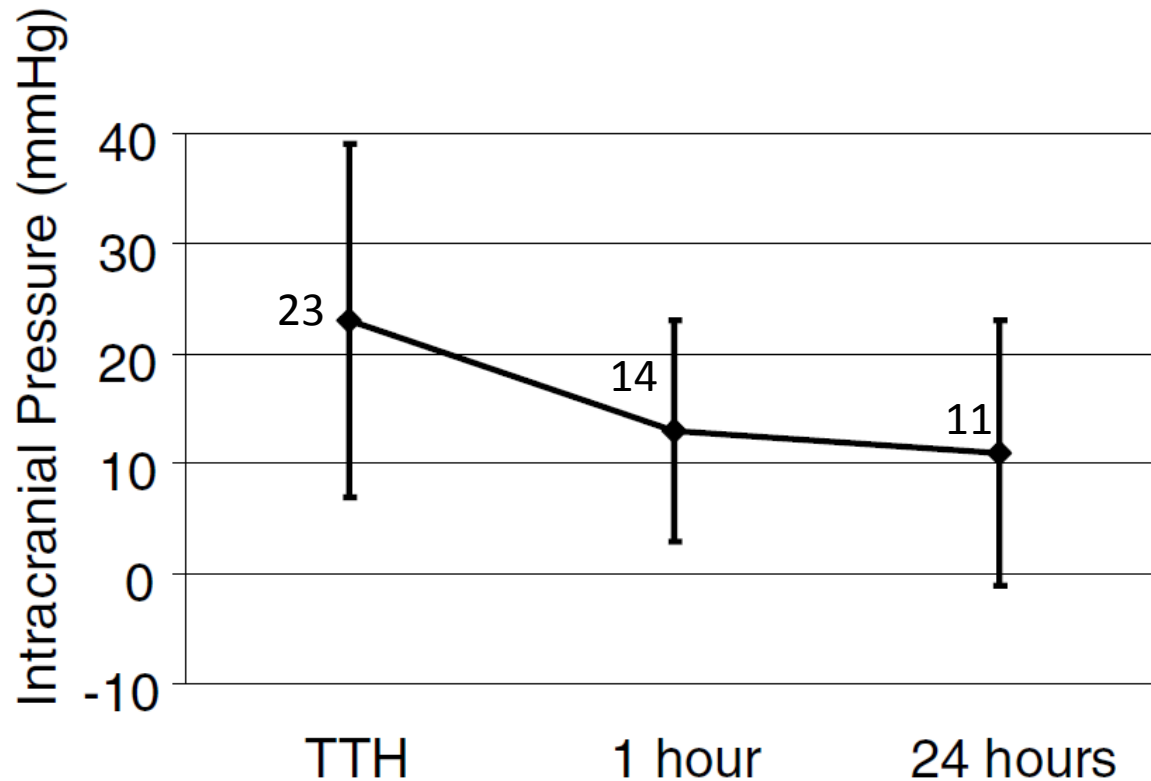


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2008年HS治疗TTH

23.4% HS 30-60ml推注, 75% (57/76) TTH逆转



TTH逆转的预测因素

Table 3 Univariable predictors of reversal of herniation

	Reversal of TTH	No reversal of TTH	p Value
Age, y	52.1 ± 14.1	52.8 ± 12.0	0.828
Hyperventilation	41/57 (71.9)	12/19 (63.2)	0.665
Propofol use	40/57 (70.2)	7/19 (36.8)	0.021*
Mannitol use	26/57 (45.6)	7/19 (36.8)	0.689
Pentobarbital use	10/57 (17.5)	1/19 (5.3)	0.347
2%/3% saline use	26/57 (45.6)	6/19 (31.6)	0.888
1-h Na >145	43/56 (76.8)	6/17 (35.3)	0.007*
1-h Na increase >5	46/54 (85.2)	4/14 (28.6)	<0.001*
Surgical decompression	10/57 (17.5)	4/19 (21.1)	1.000
Ventriculostomy	16/57 (28.1)	5/19 (26.3)	0.882
Diagnosis of ICH	19/57 (33.3)	11/19 (57.9)	0.104*



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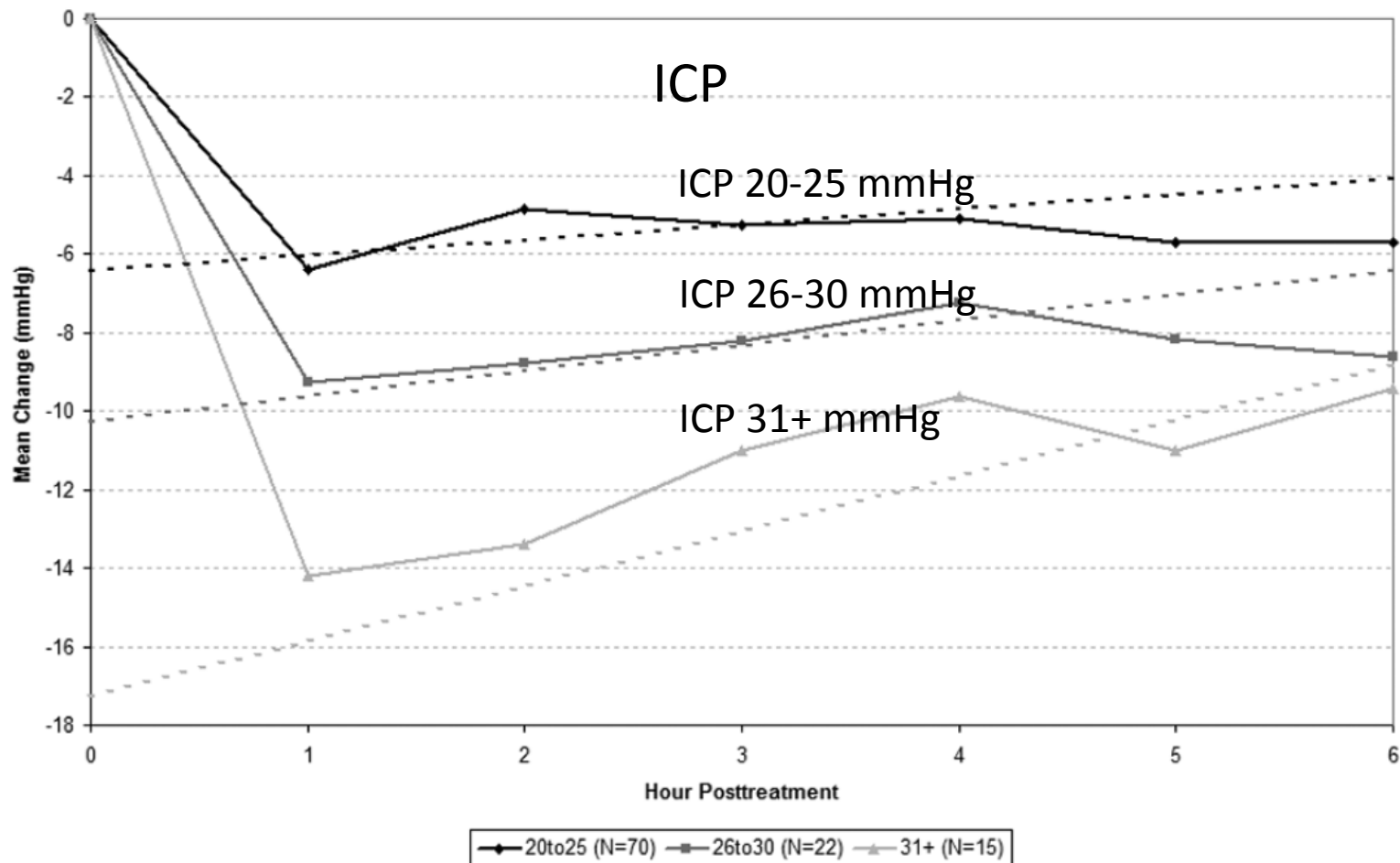


无不良事件

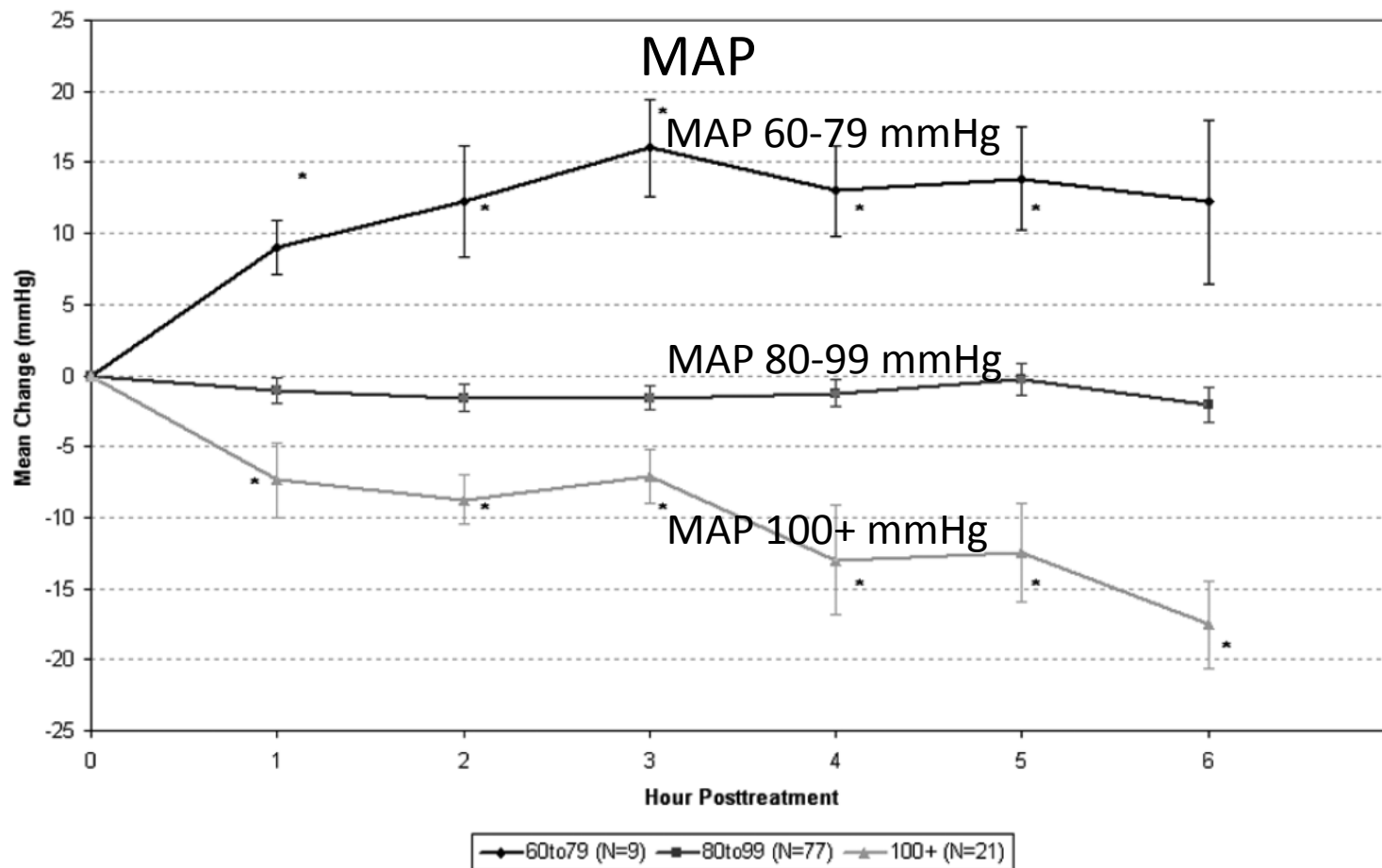
Adverse event	Clinical definition
Hypotension	MAP <60 mm Hg or MAP decrement >30 mm Hg from baseline within 1 h of treatment
Pulmonary edema	Evidence of pulmonary edema on chest x-ray obtained within 24 h of treatment
Acute renal failure	Serum creatinine >1.4 mg/dL with normal baseline or >20% increase with elevated baseline within 72 h of treatment
Hemolysis	Decrease in hemoglobin of >2 g/dL or need for packed red blood cell transfusion, and serum bilirubin elevation within 24 h of treatment
Central pontine myelinolysis	Pontine T2 or FLAIR hyperintensity with or without restricted diffusion on MRI <4 wk from treatment
Coagulopathy	Clinically relevant bleeding with unexplained elevation of INR or aPTT ratio >1.2 within 24 h of treatment
Cardiac arrhythmia	Documentation of new atrial or ventricular arrhythmia on cardiac monitor within 24 h of treatment



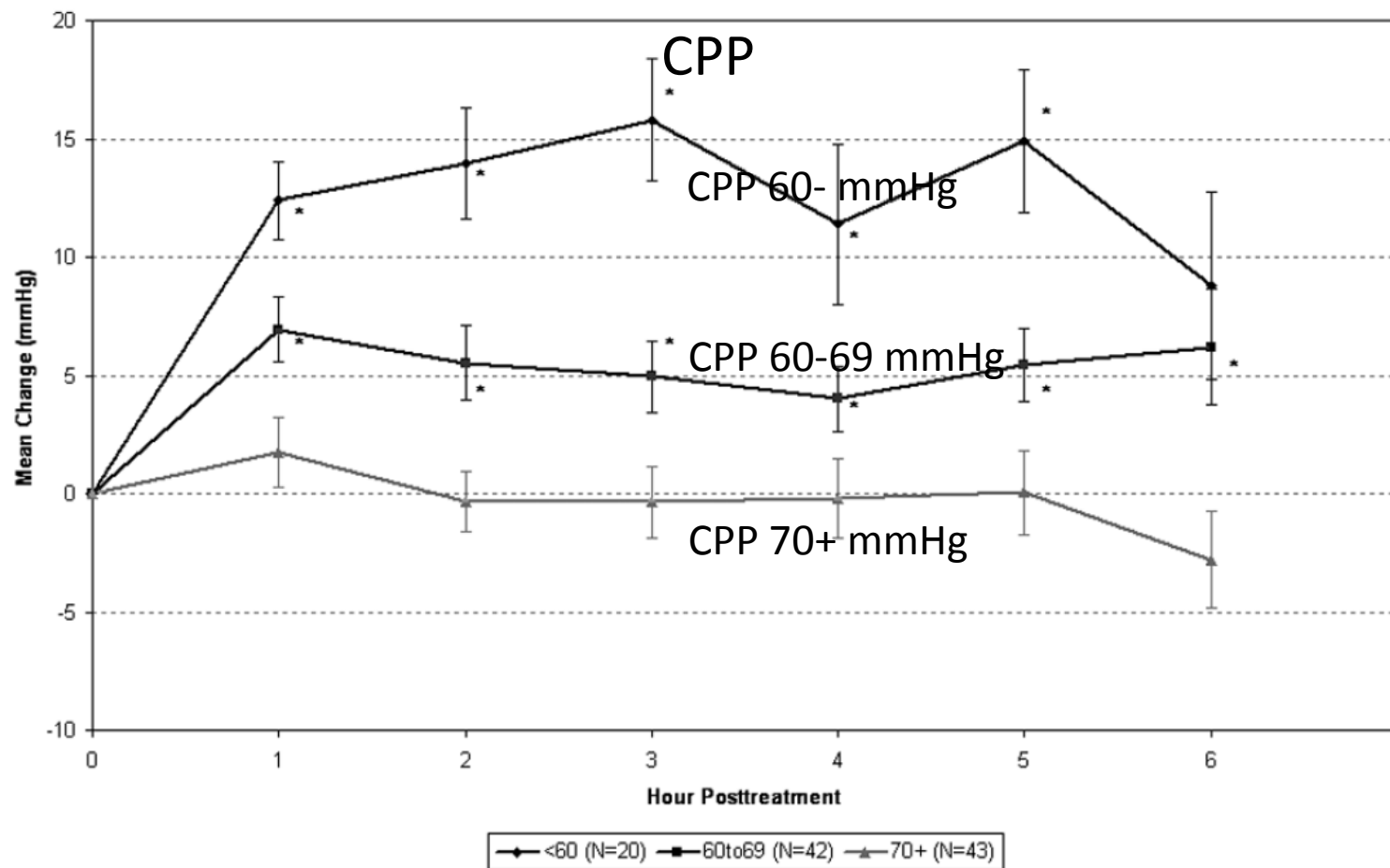
2009年TBI 23.4%HS 30ml 多参数研究



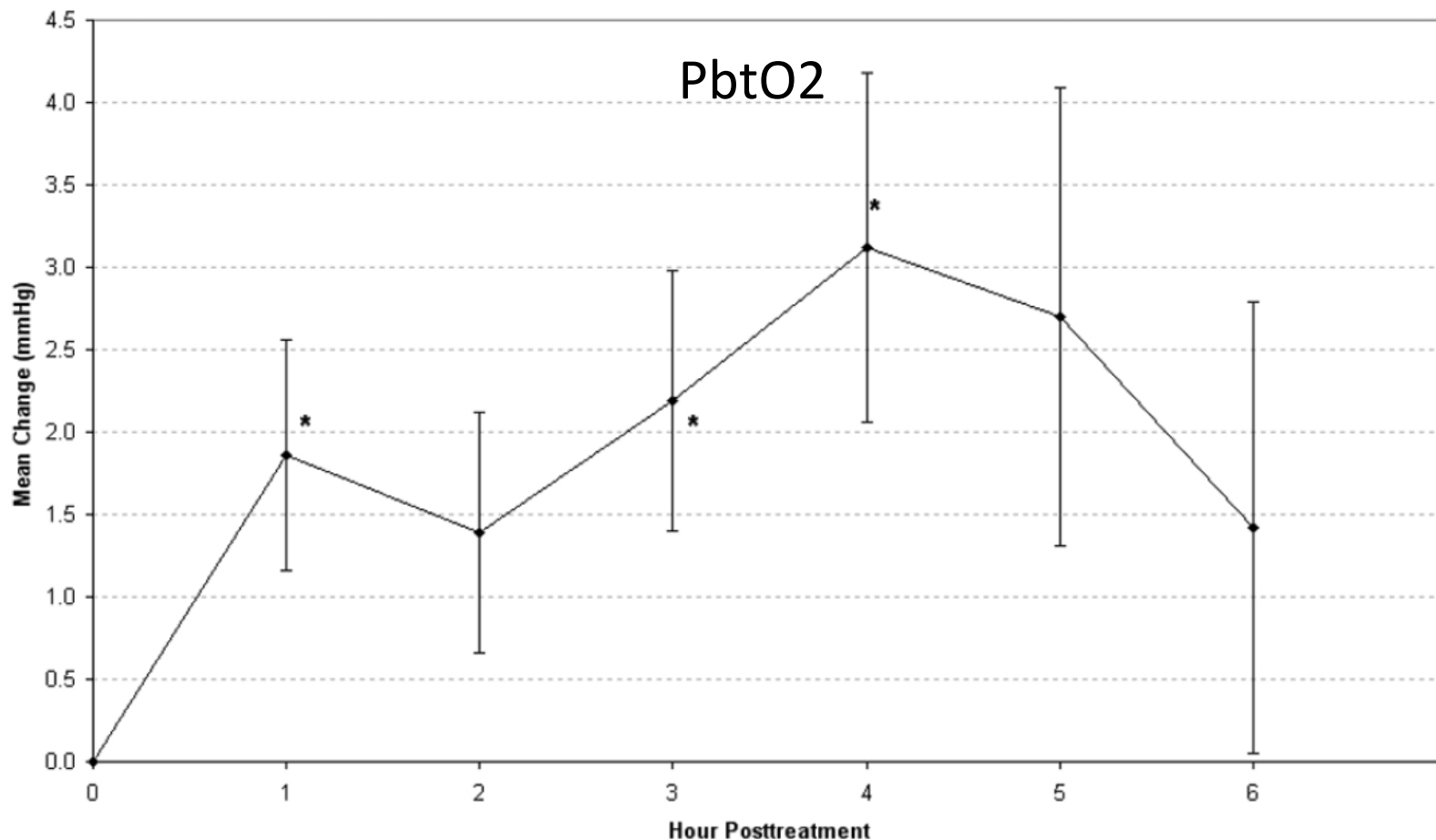
2009年TBI 23.4%HS 30ml 多参数研究



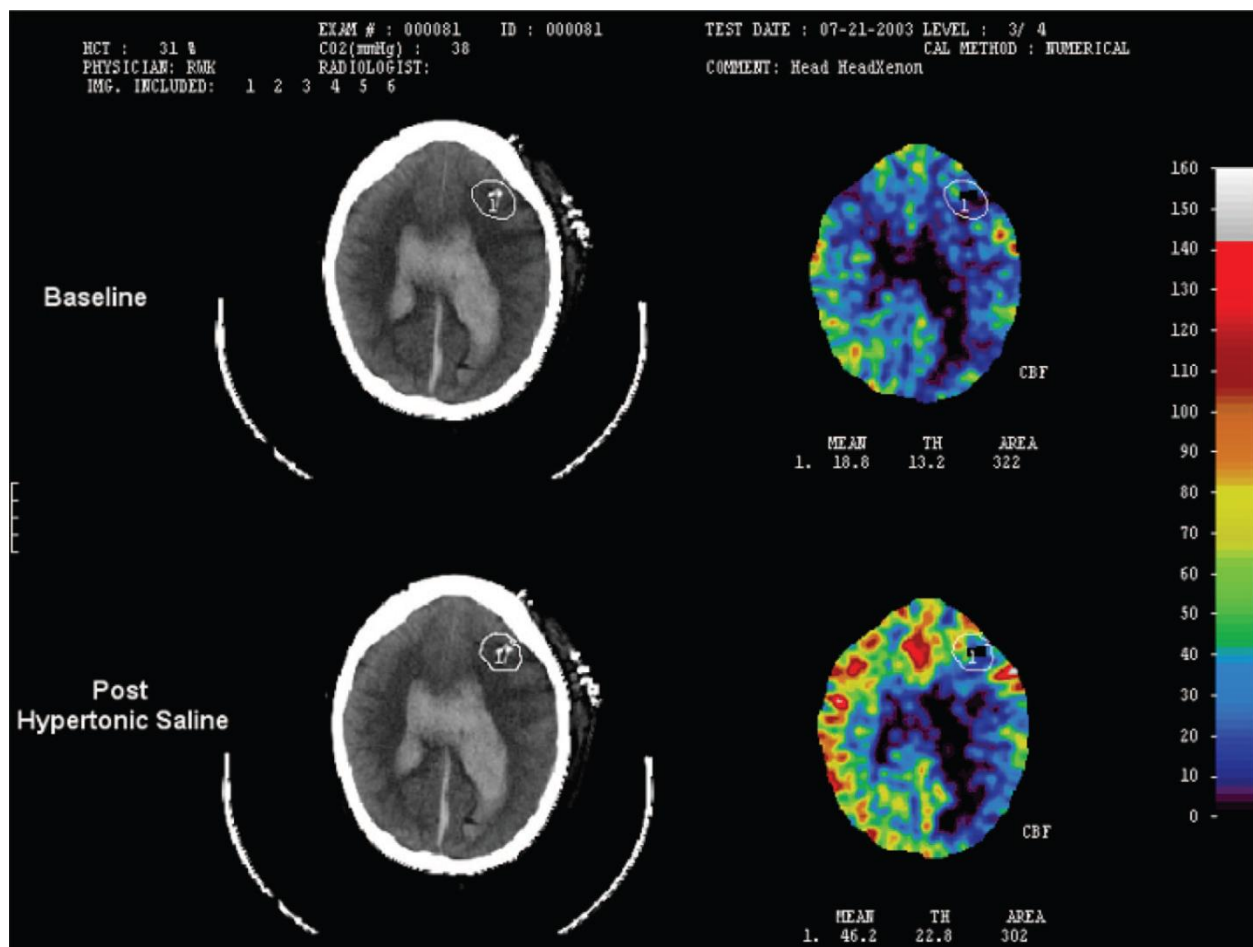
2009年TBI 23.4%HS 30ml 多参数研究



2009年TBI 23.4%HS 30ml 多参数研究



2010年SAH 23.5% HS 2ml/kg 多参数研究



2012年不同渗透压对HS的反应

Serum osmolality (mOsm/kg)	≤ 320	> 320	<i>P</i> value
Reduction to mean ICP			
Mean (mmHg)	-8.50	-9.56	0.6090
Standard error	1.03	1.97	
<i>P</i> value	< 0.0001	0.0013	
Reduction to lowest ICP measurement			
Mean (mmHg)	-11.82	-13.0	0.6384
Standard error	1.28	2.32	
<i>P</i> value	< 0.0001	0.0005	



安全性



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理论上的药物副作用

Drug	Adverse Effects
Mannitol	Rebound increase in intracranial pressure, acute renal failure, chronic heart failure, hypotension, hyperkalemia, hypernatremia
Hypertonic saline	Acute renal failure, myelinolysis, chronic heart failure, metabolic acidosis or metabolic alkalosis, rebound hyponatremia, hypokalemia, infection, anemia, coagulopathy, phlebitis, rebound increased intracranial pressure



3% (n=107) vs 0.9% (n=80) 盐水

Complications	CHS, n (%)	NS, n (%)	<i>p</i>	Adjusted Odds Ratio ^a	95% Confidence Interval	<i>p</i>
Sodium >155	56 (52.3)	13 (16.3)	<0.0001	5.30	(2.52–11.13)	<0.0001
Sodium ≤155	51 (47.7)	67 (83.8)				
Sodium >160	36 (33.6)	4 (5)	<0.0001	9.11	(2.97–27.90)	<0.0001
Sodium ≤160	71 (66.4)	76 (95)				
DVT, yes	19 (17.76)	9 (11.3)	0.2173	1.32	(0.52–3.38)	0.55
DVT, no	88 (82.2)	71 (88.7)				
Infection, yes	93 (86.9)	63 (78.8)	0.1374	1.47	(0.55–3.90)	0.44
Infection, no	14 (13.1)	17 (21.3)				
BUN >8.9	44 (41.1)	38 (47.5)	0.38	1.17	(0.59–2.32)	0.66
BUN ≤8.9	63 (58.9)	42 (52.5)				
Creatinine >132.6	23 (21.5)	23 (28.8)	0.25	0.92	(0.45–1.89)	0.82
Creatinine ≤132.6	84 (78.5)	57 (71.3)				



3% (n=107) vs 0.9% (n=80) 盐水

Complications	Na >155, n (%)	Na ≤155, n (%)	<i>p</i>	Adjusted Odds Ratio ^a	95% Confidence Interval	<i>p</i>
DVT, yes	16 (23.2)	12 (10.2)	0.02	2.30	(0.90–5.94)	0.08
DVT, no	53 (76.8)	106 (89.8)				
Infection, yes	57 (82.6)	99 (83.9)	0.82	1.09	(0.41–2.91)	0.87
Infection, no	12 (17.4)	19 (16.1)				
BUN >8.9	32 (47.8)	50 (41.7)	0.42	2.34	(1.13–4.88)	0.02
BUN ≤8.9	35 (52.2)	70 (58.3)				
Creatinine >132.6	21 (31.3)	25 (20.8)	0.11	2.82	(1.29–6.17)	0.01
Creatinine ≤132.6	46 (68.7)	95 (79.2)				

3% (n=107) vs 0.9% (n=80) 盐水

Complications	Na >160, n (%)	Na <160, n (%)	Chi-square <i>p</i>	Adjusted Odds Ratio ^a	95% Confidence Interval	Adjusted <i>p</i>
DVT, yes	9 (22.5)	19 (12.9)	0.13	1.66	(0.58–4.74)	0.34
DVT, no	31 (77.5)	128 (87.1)				
Infection, yes	34 (85.0)	122 (83.0)	0.76	1.95	(0.58–6.57)	0.28
Infection, no	6 (15.0)	25 (17.0)				
BUN >8.9	21 (52.5)	61 (41.5)	0.21	3.46	(1.48–8.06)	0.004
BUN ≤8.9	19 (47.5)	86 (58.5)				
Creatinine >132.6	12 (30.0)	34 (23.1)	0.37	2.23	(0.94–5.31)	0.07
Creatinine ≤132.6	28 (70.0)	113 (76.9)				

理论上的药物副作用

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Mannitol	Rebound increase in intracranial pressure, acute renal failure, chronic heart failure, hypotension, hyperkalemia, hypernatremia
Hypertonic saline	Acute renal failure, myelinolysis, chronic heart failure, metabolic acidosis or metabolic alkalosis, rebound hyponatremia, hypokalemia, infection, anemia, coagulopathy, phlebitis, rebound increased intracranial pressure



未来.....

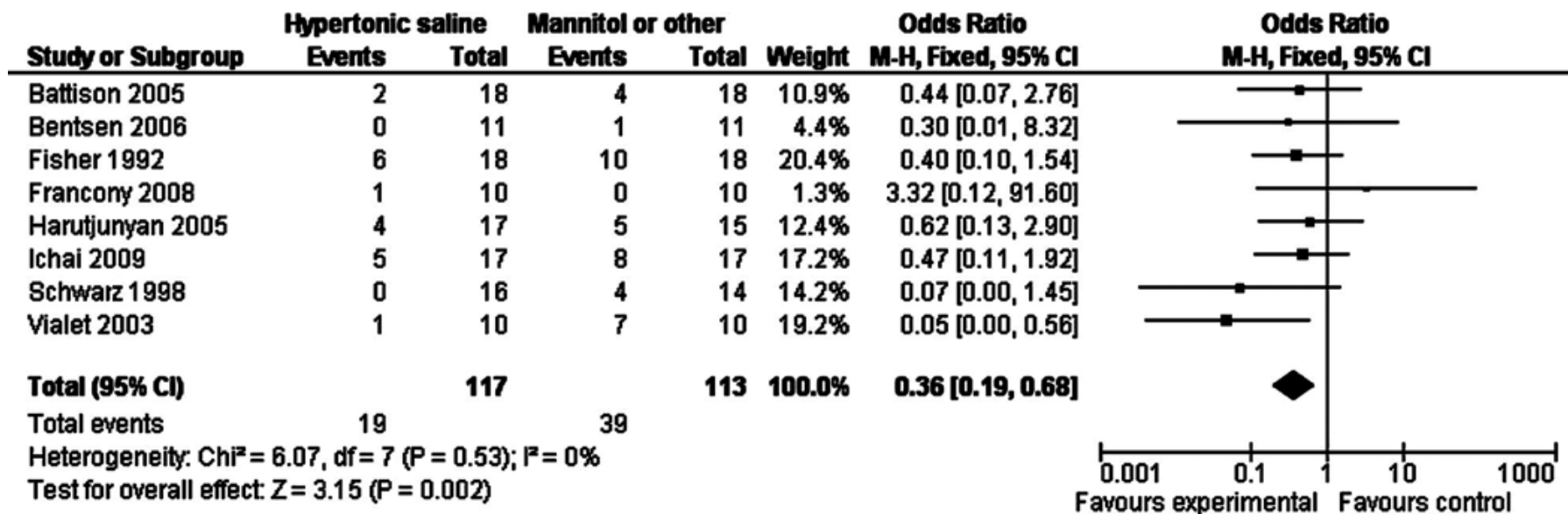


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HS优于Mannitol?

呼唤未来大样本RCT研究



未来HS面临问题

- HS 浓度, 3% (250ml) ? 7.5% (100ml) ? 10% (70ml) ? 23.4% (30ml) ?
- 剂量, 7g NaCl ? 14g NaCl ?
- 频次, PRN ? Q8h ? Q6h ? Q4h ? 先推注, 再持续滴注 ?
- 输注速度, 推注 ? 15min ?
- 输液通路, 周围静脉 ? 中心静脉
- 疾病类型 ? TBI ? SAH ? ICH ? 恶性水肿 ?
- 血钠的监测, q4h ? Q12h ?
- 血钠上升的速度 ? 迅速升高导致渗透性脑病 ?
- 最佳血钠水平, 150 ? 155 ? 160mmol/l ? 更高 ?
- 最佳渗透压 (BEST TRIP TRIAL) :
 - 甘露醇要求 < 320mOsm/l ?
 - 高张盐水要求 < 360mOsm/l ?



谢谢



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