India


India
IRAN
AFGHANISTAN
PAKISTAN
CHINA
TIBET
Srinagar
Boundaries in dispute
Amritsar
Ludhiana
Chandigarh
Delhi
New Delhi
Moradabad
Agra
Jaipur
Jodhpur
Kanpur
Lucknow
Allahabad
Varanasi
Thar Desert
Indus
Brahmaputra
Mt. Everest
NEPAL
BHUTAN
Gangtok
Darjeeling
Shillong
Imphal
BANG
Persian Gulf
Tropic of Cancer
U.A.E.
Gulf of Oman
SAUDI ARABIA
OMAN
20° N
Ahmadabad
Vadodara
Bhavnagar
Surat
Nashik
Bhopal
Indore
Nagpur
Jabalpur
Jamshedpur
Raipur
Bhilai
Calcutta
Cuttack
Godavari
Mumbai (Bombay)
Pune
Ahmadnagar
Solapur
Arabian Sea
Krishna
Hyderabad
Visakhapatnam
Kakinada
Vijayawada
Bay of Bengal
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0 300 Miles
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Hubli
Kurnool
Nellore
Mangalore
Chennai (Madras)
Andaman Islands (INDIA)
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Mysore
Bangalore
Port Blair
Kozhikode
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Optimum sodium levels in children with brain injury

Professor Sunit Singhi,

Head ,

Department of Pediatrics,

Head, Pediatric

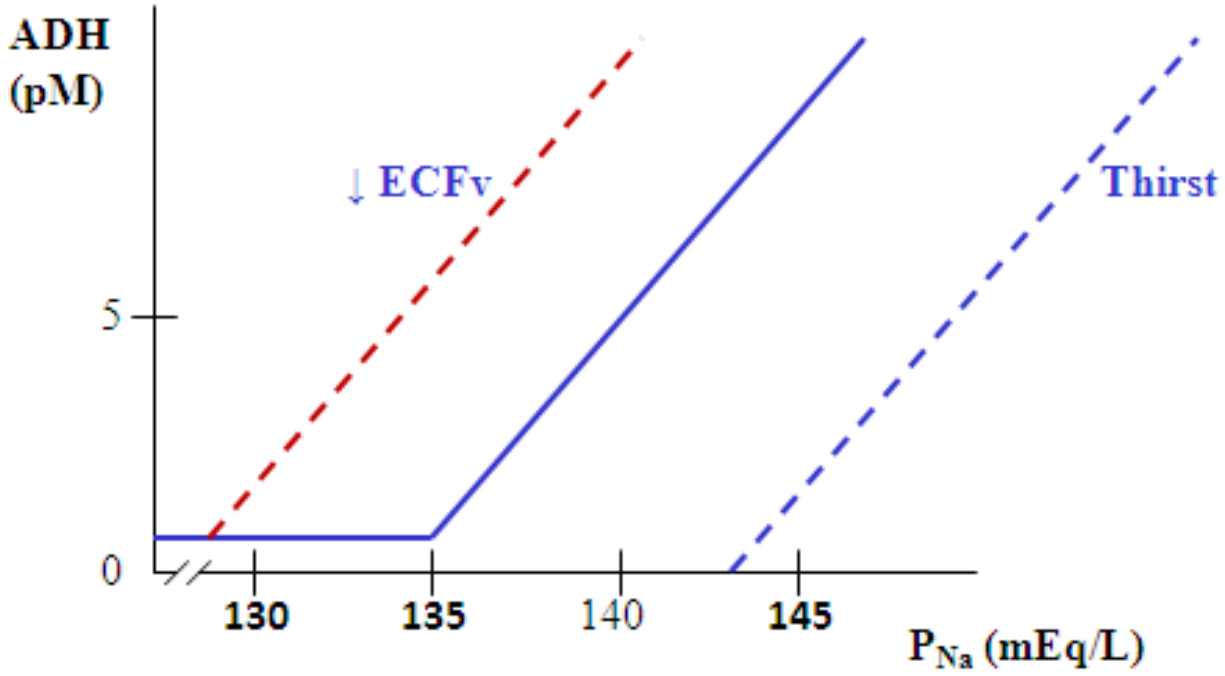
Sodium and brain

- *Sodium* - the major extracellular cation and most important osmotically active solute

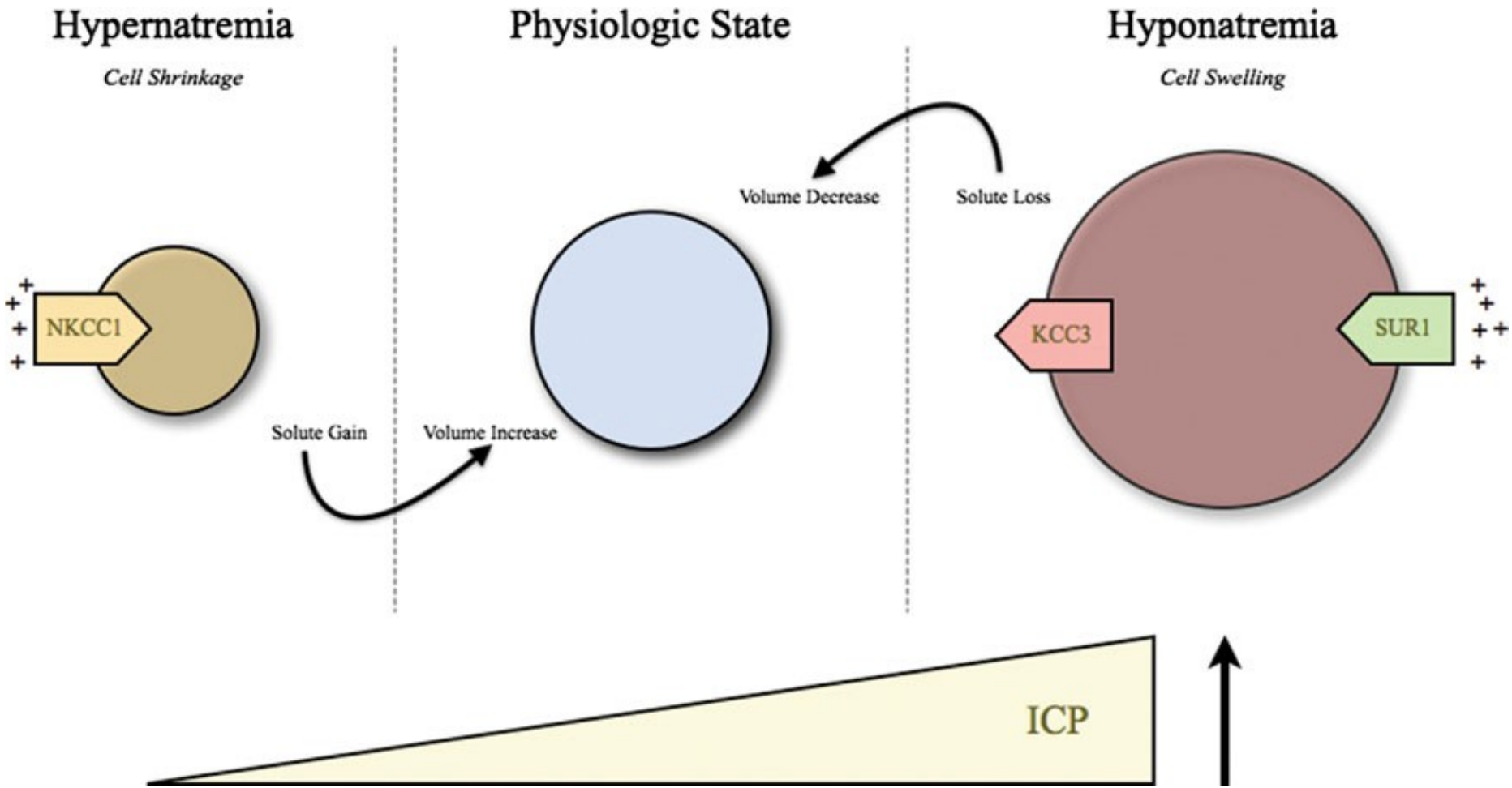
Regulation of serum sodium

- Sodium regulation is closely correlated with the body's **effective circulating volume (ECV)**

  (intravascular volume to provide adequate tissue perfusion)
- Major determinant of Sr.Na is in fact **serum water content**.

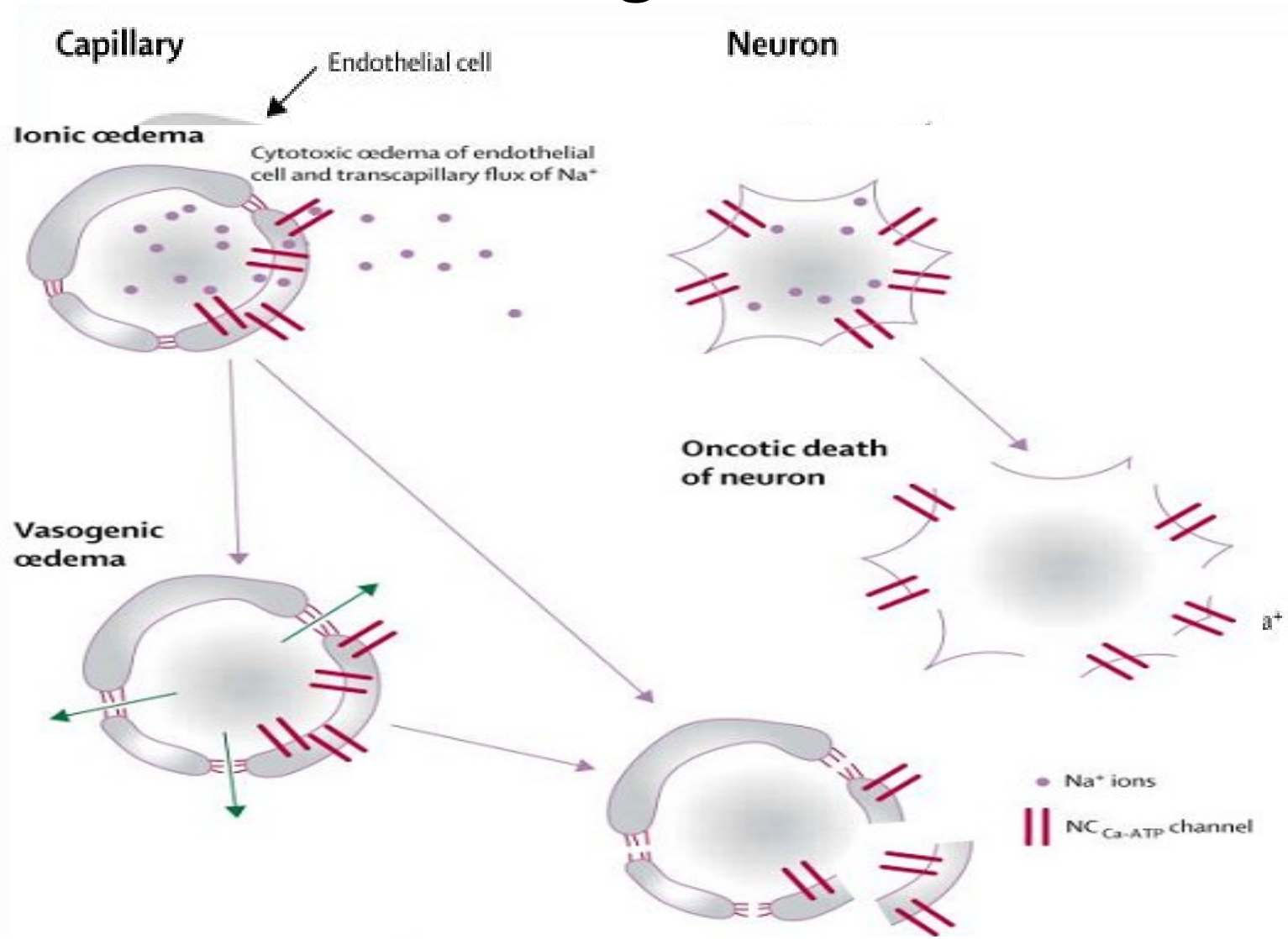


Cerebral Physiology



- **Ion transporters** are key mediators of cell volume and respond to both cell shrinkage and cellular swelling.

Secondary cerebral swelling progressing to hemorrhagic conversion



Optimal Sodium in patients with brain injury

- **Evidence 1**

Serum Sodium needs to be >135 meq/L

Hyponatremia in patients with brain injury

- Fairly often observed in children with traumatic brain injury

(Acute symptomatic hyponatremia and cerebral salt wasting after head injury: an important clinical entity. *J Pediatr Surg. 2001)*

- 7 to 32% of patients with different forms of meningitis

SIADH

Euvolemic hyponatremia

Cerebral Salt Wasting

Hypovolemic hyponatremia

(Most of the published reports from children, SIADH in older studies, CSW emerging in recent literature)

The distinction is blurred

Hyponatremia in patients with brain injury

‘Serum sodium < 135 mEq/L is detrimental’

- Severe hyponatremia is associated with increased risk of symptomatic vasospasm and infarctions
- potentiates secondary brain damage by augmentation of both focal contusion and diffuse axonal injury
- Affects cognitive outcome after traumatic brain injury

(Hyponatremia associated cognitive impairment in traumatic brain injury. *Brain Inj.* 1993)

Associated with poor outcome and increase in mortality upto 60%

Prevalence of hyponatraemia in critical care settings

- **Hypotonic hyponatraemia**: (excess water in ECF)

  - Greatest relevance to the critical care setting

  - Upto three quarters of ICU- hyponatraemia cases

-Bennani SL et al. Rev Med Interne. 2003.

-Adler SM. Endocrinol Metab Clin North Am. 2006.

- Friedman B et al. Journal of Critical Care. 2013.

- Frequency at admission: 10% to 14% based on severity.

-Bennani SL et al. Rev Med Interne. 2003.

- Funk GC et al. Intensive Care Med 2010.

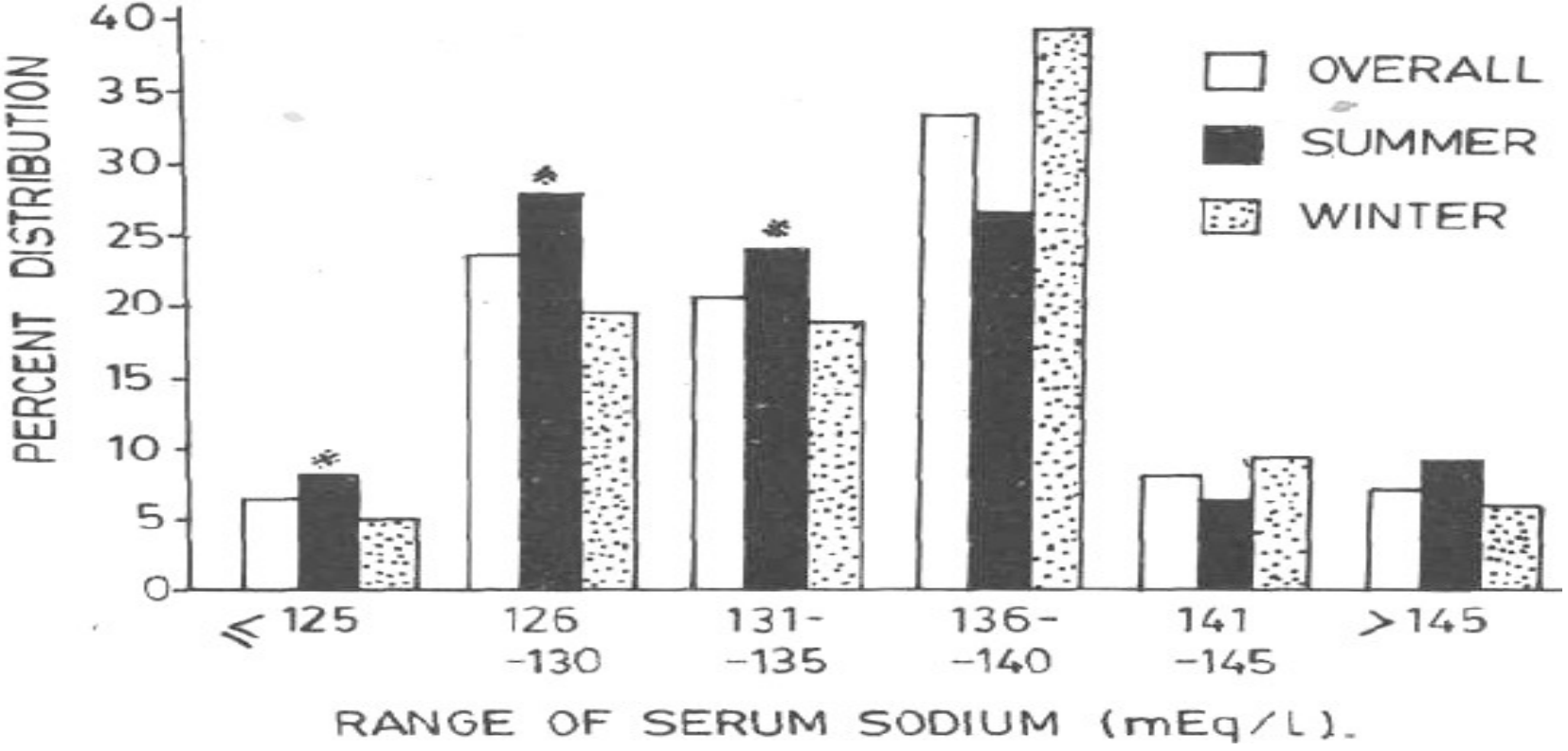
- Prevalence of hyponatraemia in ICU: as high as 30% to 40%.

-Friedman B et al. Journal of Critical Care. 2013.

Prevalence of hyponatraemia in critical care settings in children

- Recent study in 1440 acute brain injury patients, found that 17% had mean Sr.Na of **131.8 ± 2.9**.

In our unit. (Singhi et al. Indian Pediatr.1994)



Outcome of hyponatraemia in critical care settings

- **All forms** of hyponatraemia is a **strong independent predictor** of mortality, reported to be as high as 60% in some series.

  -Friedman B et al. Journal of Critical Care. 2013.

  -Wald R et al. Arch Intern Med. 2010.

  - Cowen LE et al. Endocrinol Metab Clin N Am.2013.

- The relative risk of in-hospital mortality associated with admission hyponatraemia was significantly increased at 2.0.

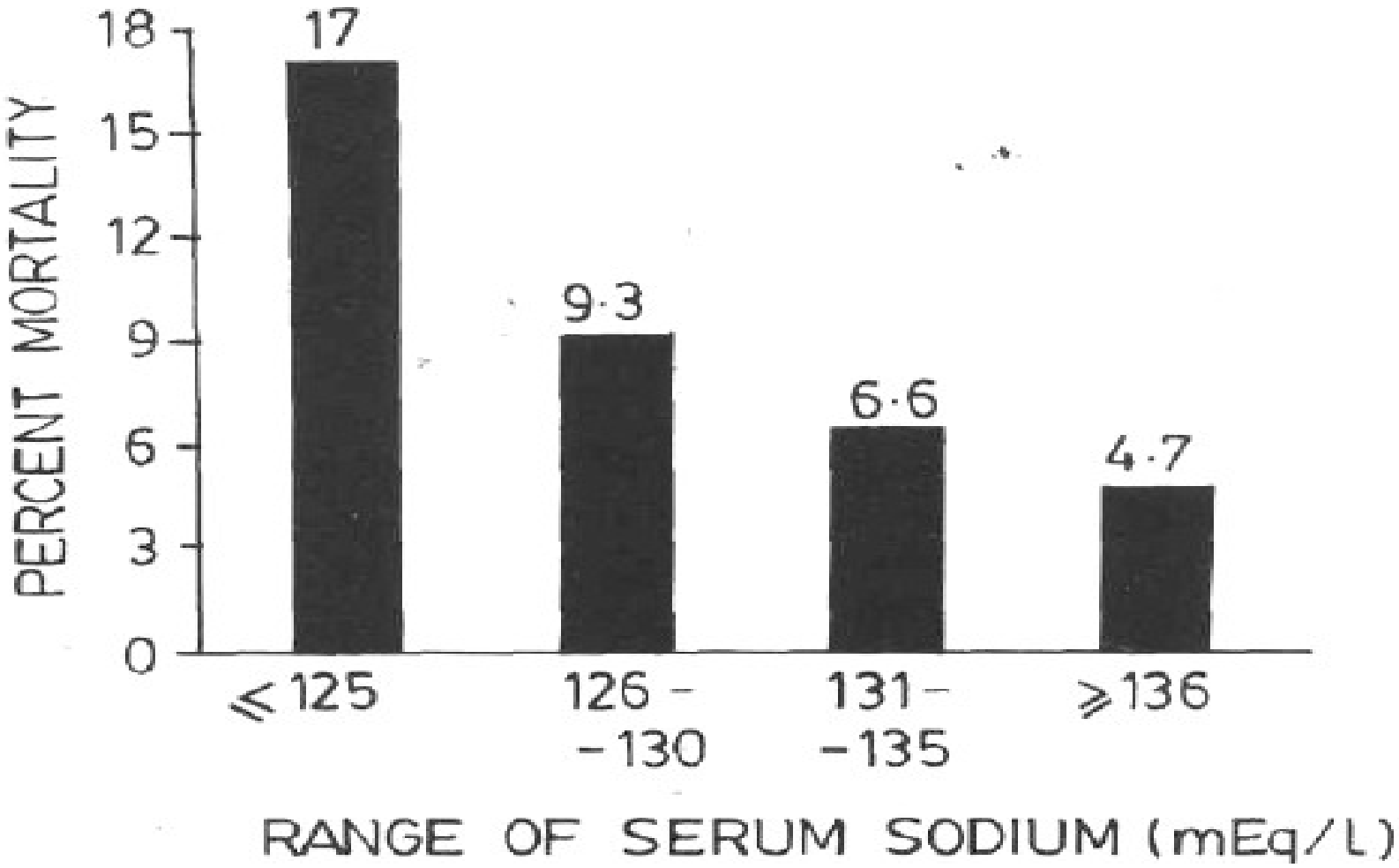
  - Cowen LE et al. Endocrinol Metab Clin N Am.2013.

- Median (IQR) ICU stays prolonged upto 4 (2 to 8) days.

  -Stelfox HT et al. Crti Care.2008.

Outcome of hyponatraemia in critical care settings

In our unit, (Singhi et al, Indian Pediatr.1994)



Outcome of hyponatraemia in critical care settings : Benefits of resolution

Waikar SS et al. Am J Med. 2009.

Mortality after Hospitalization with Hyponatremia.

- In a prospective cohort study of **98 411** adults in Boston.

	Sodium Concentration (mEq/L)					
	135-144 (n = 82,377)	<135 (n = 12,562)	130-134 (n = 10,469)	125-129 (n = 1591)	120-124 (n = 353)	<120 (n = 149)
Crude in-hospital mortality (%)	2.4	5.4	4.8	8.9	8.5	6.7
Multivariable-adjusted	1 (ref)	1.47 (1.33-1.62)	1.37 (1.23-1.52)	2.01 (1.64-2.45)	1.67 (1.09-2.56)	1.46 (0.73-2.91)
Crude 1-year mortality (%)	11.7	21.4	19.8	28.5	33.1	22.2
Multivariable-adjusted	1 (ref)	1.38 (1.32-1.46)	1.35 (1.28-1.43)	1.53 (1.36-1.71)	1.78 (1.44-2.21)	1.03 (0.68-1.56)
Crude 5-year mortality (%)	42.3	54.8	53.6	61.0	60.6	59.7
Multivariable-adjusted	1 (ref)	1.25 (1.21-1.30)	1.24 (1.19-1.29)	1.33 (1.23-1.44)	1.29 (1.09-1.53)	1.09 (0.84-1.41)

Optimal Sodium in patients with brain injury

- **Evidence 1**

Serum Sodium needs to be >135 meq/L

Hypernatremia in patients with cerebral injury

- Increased insensible water loss
- Inadequate provision of free water (impaired thirst, limited access)
- Development of Central DI
- Improper isotonic saline therapy

Hypernatremia in critically ill- Frequency & timing

Author and year	Study type	Serum sodium cutoff defining hypernatremia	Population size (N)	ICU type	Incidence of ICU-acquired hypernatremia
Lindner et al [13]	Retrospective	145 mmol/L	2.314	Surgical	10%
Stelfox et al [15]	Retrospective	145 mmol/L	6.727	Surgical	4%
Darmon et al [12]	Retrospective	145 mmol/L	8.441	Mixed	11% (mild) 4% (moderate to severe)
O'Donoghue et al [16]	Retrospective	150 mmol/L	3.317	Mixed	8%
Stelfox et al [14]	Retrospective	145 mmol/L	8.142	Mixed	26%
Hoorn et al [45]	Retrospective	150 mmol/L	1.843	Mixed	7%
Lindner et al [10]	Retrospective	150 mmol/L	981	Medical	7%
Polderman et al [76]	Retrospective	150 mmol/L	389	Medical	6%

- Average duration of hypernatremia was 2 days (range, 1 to 10)

- Lindner G. Am J Kidney Dis. 2009

Hypernatremia in neurointensive care units

Aiyagari V et al - Journal of Critical Care

- Retrospective analysis of pro[illegible]ollected data in patients admitted to the NNIC[illegible]-year period.
- Hypernatremia (>150 mEq[illegible] in 339 patients (7.9%).
- More common (24.3%[illegible] treated with mannitol.

Stelfox HT et al. Cri[illegible]08

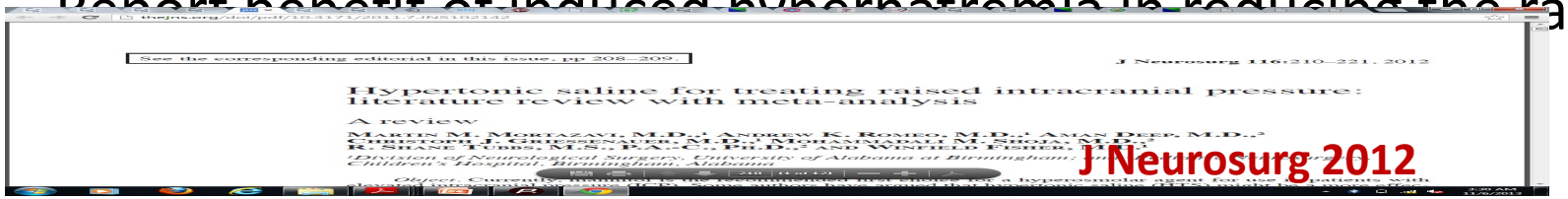
- ICU-acquired [illegible]mia in medical-surgical ICU (n=8142)
- A first ep[illegible]natremia in 2157 (26%) patients.
- Mean (SD) s[illegible]n was 149 (3.6).
- Median (IQR) time to develop hypernatremia 2 (1 to 3) days.

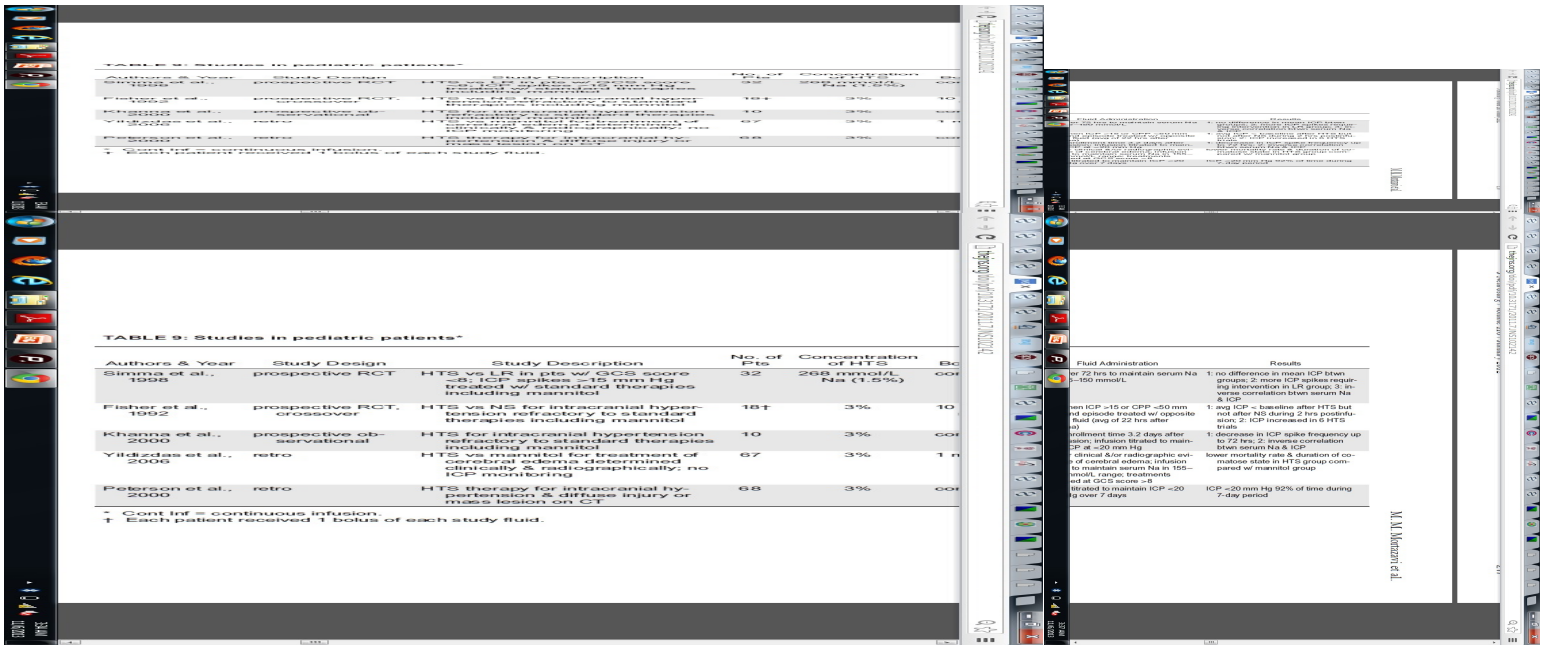
No prospective data available on NNICU- acquired hypernatremia

Hypernatremia – therapy induced

Several other studies..

Report benefit of induced hypernatremia in reducing the raised





Optimal Sodium in patients with brain injury

- **Evidence 1**

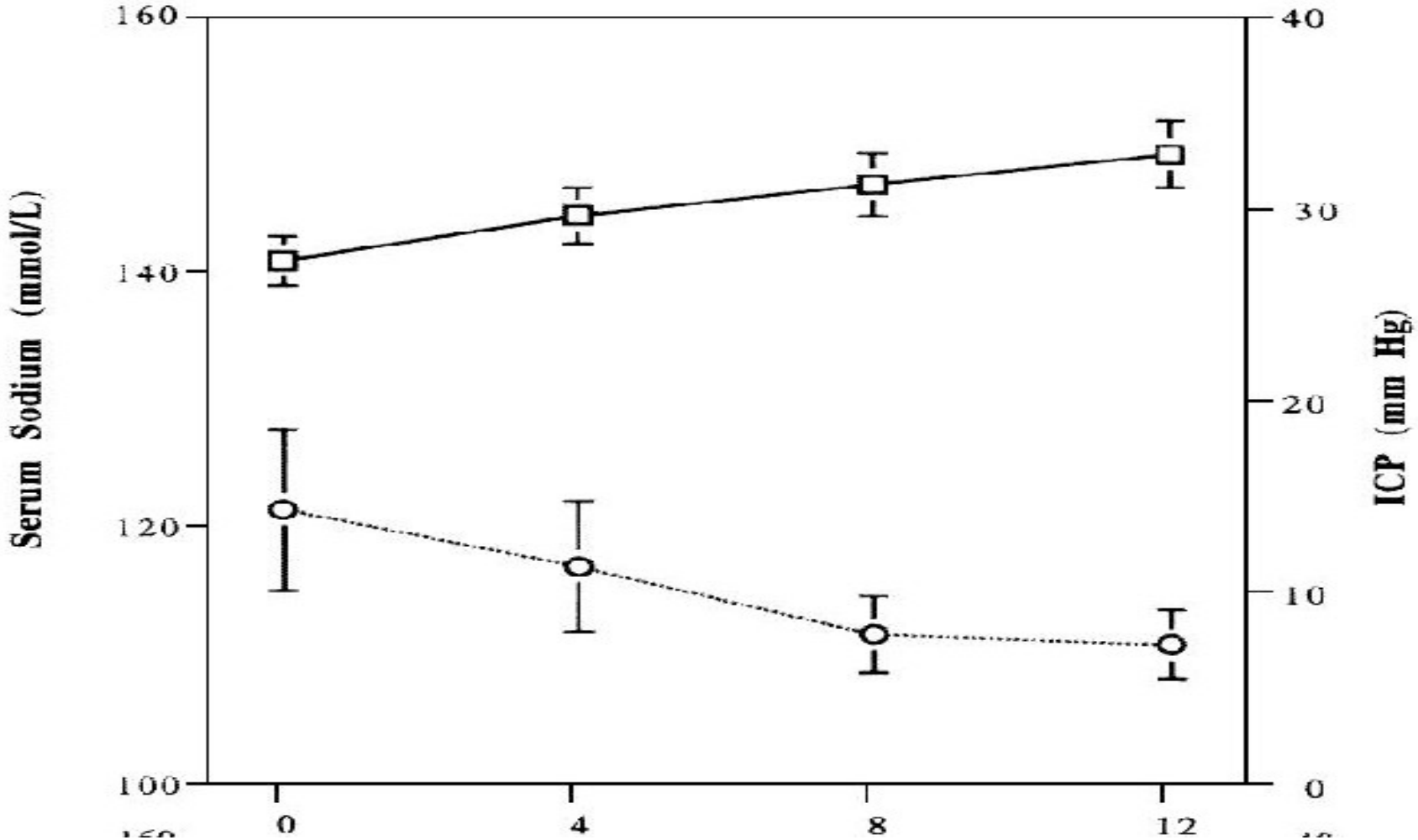
Serum Sodium needs to be >135 meq/L

- **Evidence 2**

Hypernatremia and the resultant hyperosmolarity reduces the raised intracranial pressure

Effects on injured brain: Clinical Significance

Targeted Hypernatremia in Traumatic Brain Injury

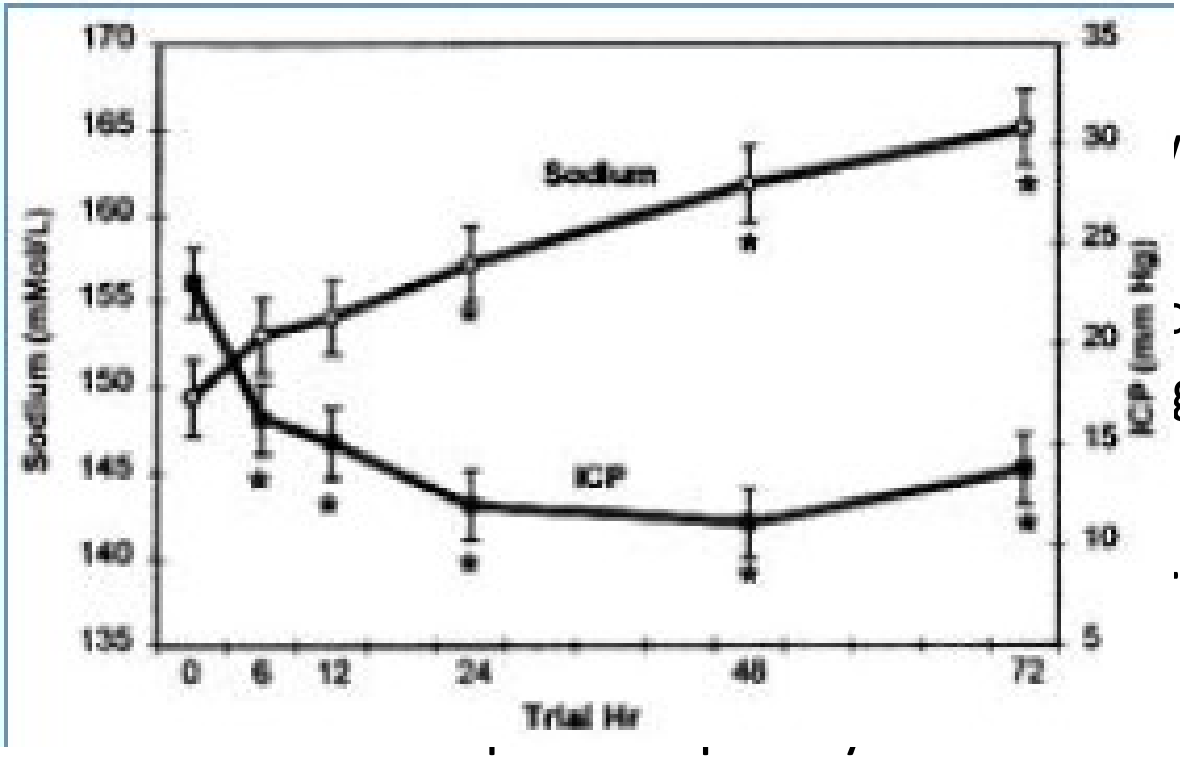


patients

Effects on injured brain: Clinical Significance

Targeted Hypernatremia in Traumatic Brain Injury

Khanna et al. Crit Care Med. 2000.



ith TBI (n=10).

dium serum levels g.

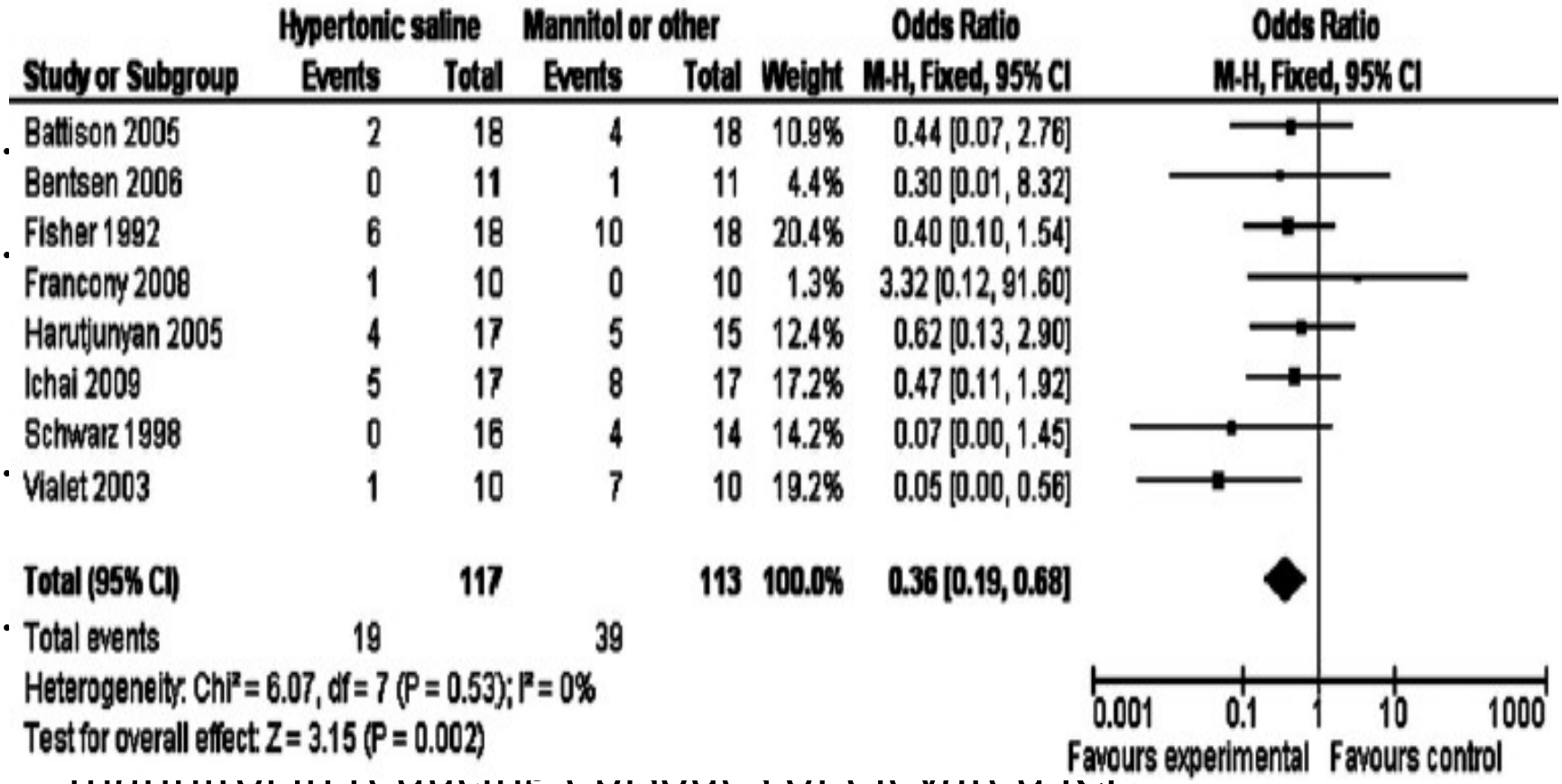
(157-187 mEq/L).

- Increased CPP compared with time zero.

Effects on injured brain: Clinical Significance

Hypertonic saline for treating raised intracranial pressure:

literature review with meta-analysis



Study or Subgroup	Hypertonic saline Events	Total	Mannitol or other Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Battison 2005	2	18	4	18	10.9%	0.44 [0.07, 2.76]
Bentsen 2006	0	11	1	11	4.4%	0.30 [0.01, 8.32]
Fisher 1992	6	18	10	18	20.4%	0.40 [0.10, 1.54]
Francony 2008	1	10	0	10	1.3%	3.32 [0.12, 91.60]
Harutjunyan 2005	4	17	5	15	12.4%	0.62 [0.13, 2.90]
Ichai 2009	5	17	8	17	17.2%	0.47 [0.11, 1.92]
Schwarz 1998	0	16	4	14	14.2%	0.07 [0.00, 1.45]
Vialet 2003	1	10	7	10	19.2%	0.05 [0.00, 0.56]
Total (95% CI)		**117**		**113**	**100.0%**	**0.36 [0.19, 0.68]**
Total events	19		39			

Heterogeneity: Chi² = 6.07, df = 7 (P = 0.53); I² = 0%

Test for overall effect: Z = 3.15 (P = 0.002)

- mannitol in reducing episodes of elevated ICP.
- Higher rate of treatment failure or insufficiency with mannitol

Effects on injured brain: Clinical Significance

Targeted Hypernatremia in <u>Non-traumatic</u> Brain Injury

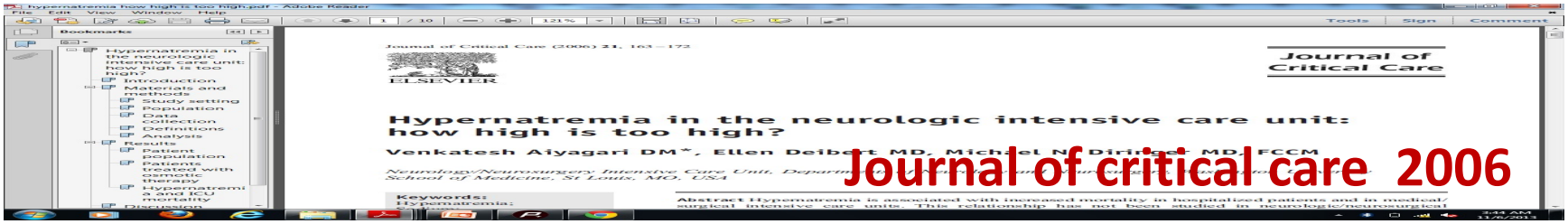
Yildizdas et al. Indian Pediatr. 2006.

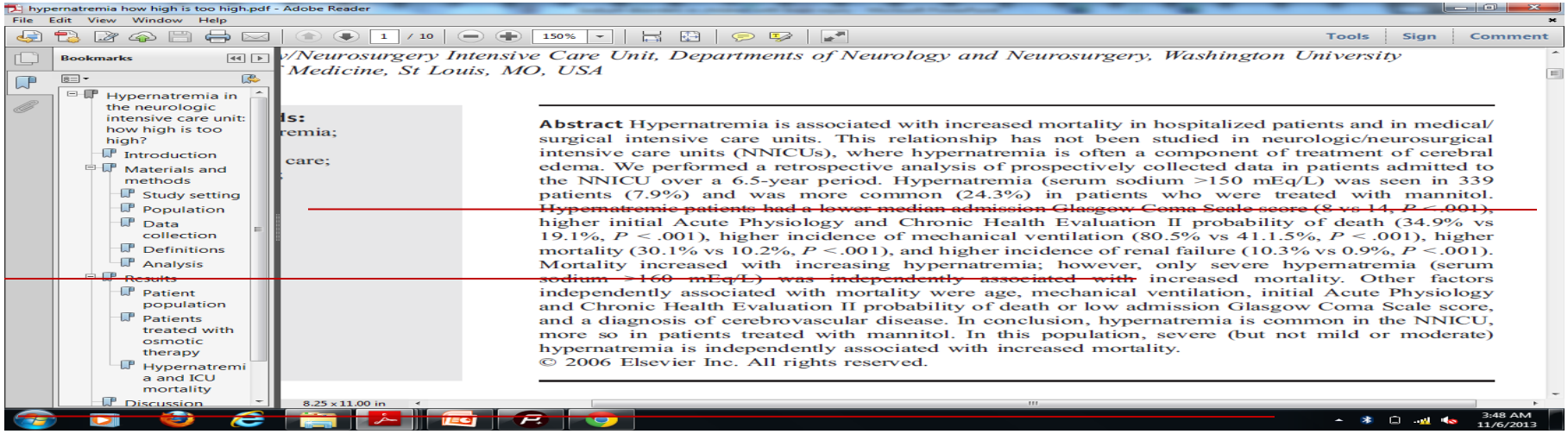
- Retrospective study, **Children** with mixed etiology.
- 3%-HST in n=25 or mannitol in=25 or both n=20.
- Target sodium **<u>155 – 165 mEq/L</u>**.
- Duration of coma and mortality was not different in patients with serum-Na of ***150-160 mEqL vs 160-170 mEqL***.

Effects on injured brain: Clinical Significance

Upadhyay P et al. J Pediatr Neurosci. 2010.

- RCT, 3%-HTS vs 20%-mannitol in **198 children** with raised ICP.
- Mean sodium in HTS-group was **136 (range 122 – 153).**
- Decrease in MAP was highly significant ($P<0.001$) at 0 h ,6 h and moderately significant at 12,24,36,42 h in HTS-group.
- Decrease in coma hours was a significant in HTS-group.
- Change in blood biochemistry was within acceptable limits.


Journal of Critical Care (2006) 21, 163–172
ELSEVIER
Journal of Critical Care
Hypernatremia in the neurologic intensive care unit: how high is too high?
Venkatesh Aiyagari DM*, Ellen Deibert MD, Michael N. Diringer MD, FCCM
Neurology/Neurosurgery Intensive Care Unit, Departments of Neurology and Neurosurgery, Washington University School of Medicine, St Louis, MO, USA
Abstract Hypernatremia is associated with increased mortality in hospitalized patients and in medical/surgical intensive care units. This relationship has not been studied in neurologic/neurosurgical
Journal of critical care 2006


hypernatremia how high is too high.pdf - Adobe Reader
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Hypernatremia in the neurologic intensive care unit: how high is too high?
Introduction
Materials and methods
Study setting
Population
Data collection
Definitions
Analysis
Results
Patient population
Patients treated with osmotic therapy
Hypernatremia and ICU mortality
Discussion
Medicine, St Louis, MO, USA
Abstract Hypernatremia is associated with increased mortality in hospitalized patients and in medical/surgical intensive care units. This relationship has not been studied in neurologic/neurosurgical intensive care units (NNICUs), where hypernatremia is often a component of treatment of cerebral edema. We performed a retrospective analysis of prospectively collected data in patients admitted to the NNICU over a 6.5-year period. Hypernatremia (serum sodium >150 mEq/L) was seen in 339 patients (7.9%) and was more common (24.3%) in patients who were treated with mannitol. Hypernatremic patients had a lower median admission Glasgow Coma Scale score (8 vs 14, P <.001), higher initial Acute Physiology and Chronic Health Evaluation II probability of death (34.9% vs 19.1%, P < .001), higher incidence of mechanical ventilation (80.5% vs 41.1.5%, P < .001), higher mortality (30.1% vs 10.2%, P <.001), and higher incidence of renal failure (10.3% vs 0.9%, P <.001). Mortality increased with increasing hypernatremia; however, only severe hypernatremia (serum sodium >160 mEq/L) was independently associated with increased mortality. Other factors independently associated with mortality were age, mechanical ventilation, initial Acute Physiology and Chronic Health Evaluation II probability of death or low admission Glasgow Coma Scale score, and a diagnosis of cerebrovascular disease. In conclusion, hypernatremia is common in the NNICU, more so in patients treated with mannitol. In this population, severe (but not mild or moderate) hypernatremia is independently associated with increased mortality.
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11/6/2013

Optimal Sodium in patients with brain injury

- **Evidence 1**

Serum Sodium needs to be >135 meq/L

- **Evidence 2**

Hypernatremia and the resultant hyperosmolarity reduces the raised intracranial pressure

- **Evidence 3**

Severe hypernatremia (? > 160 meq/L) may be

Hypernatremia – therapy induced

Crit Care Med 2000

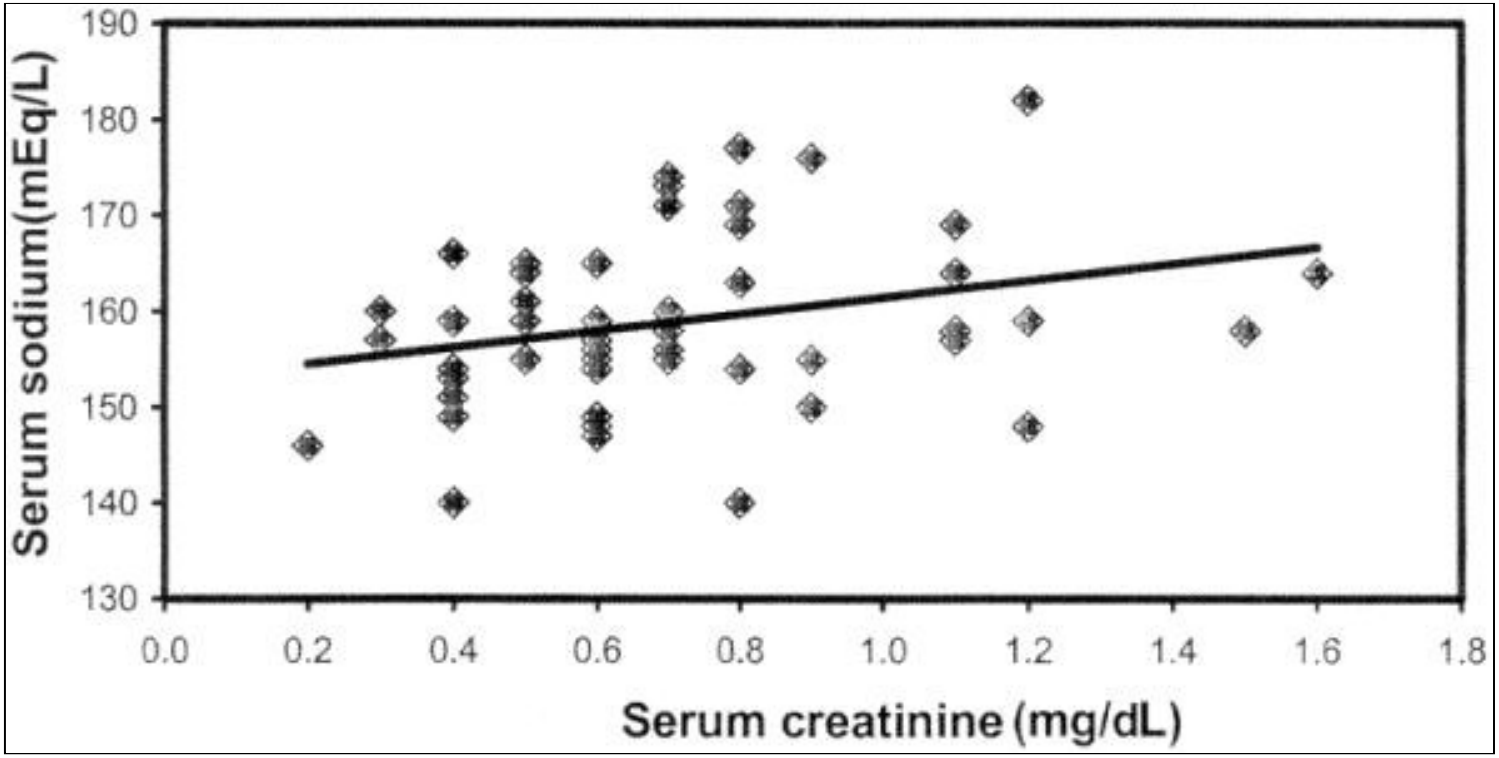
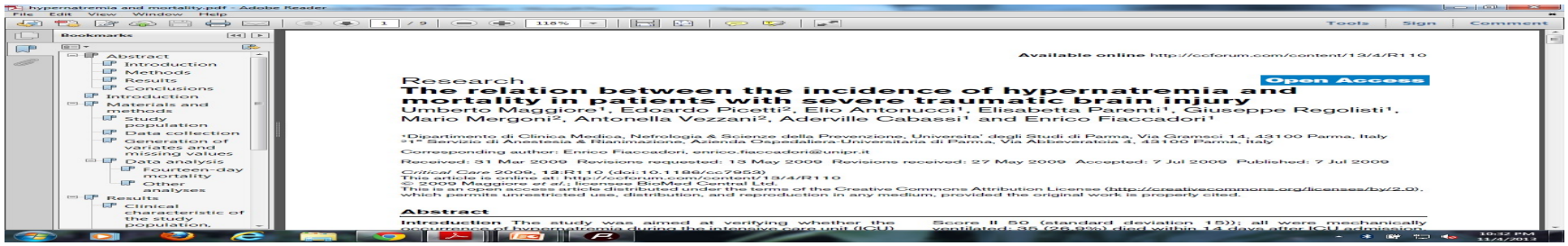
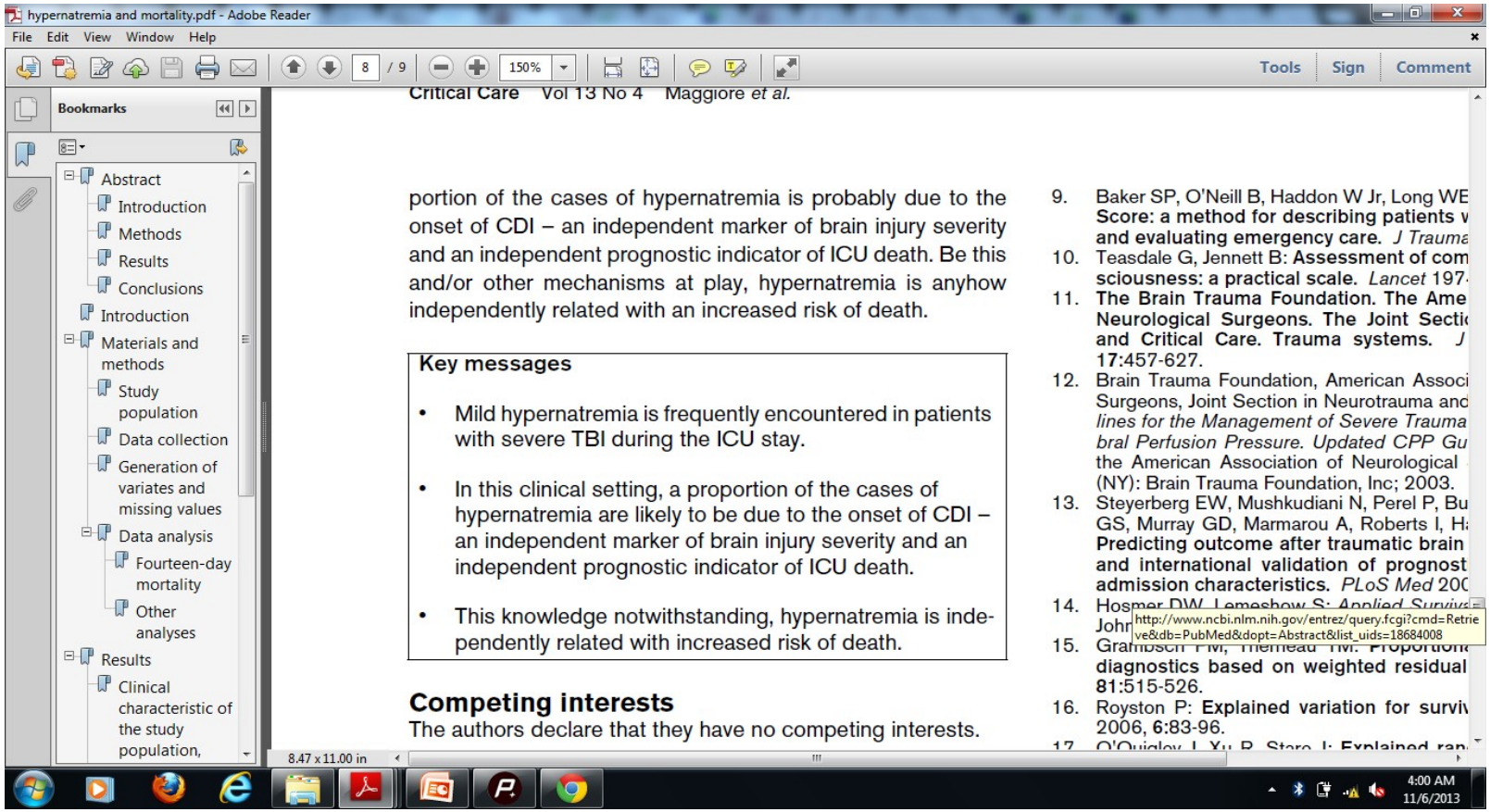
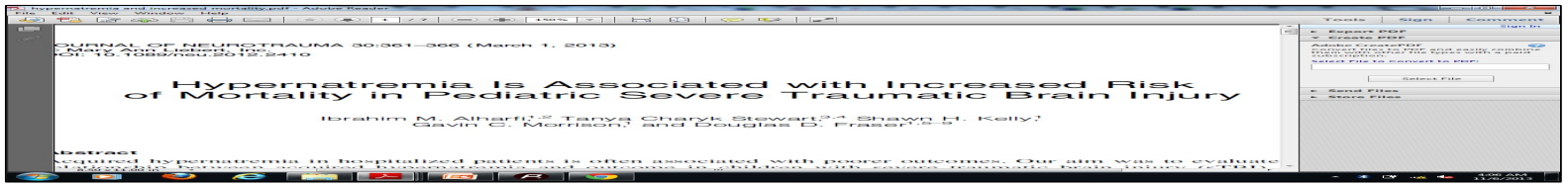


Figure 1 . Scattergram showing the relation ship between serum sodium (mEq/L) and serum creatinine (mg/dL). As serum sodium increased serum creatinine also increased. Pearson's correlation coefficient was positive for this relationship (r2 = 0.18).



Critical care 2009



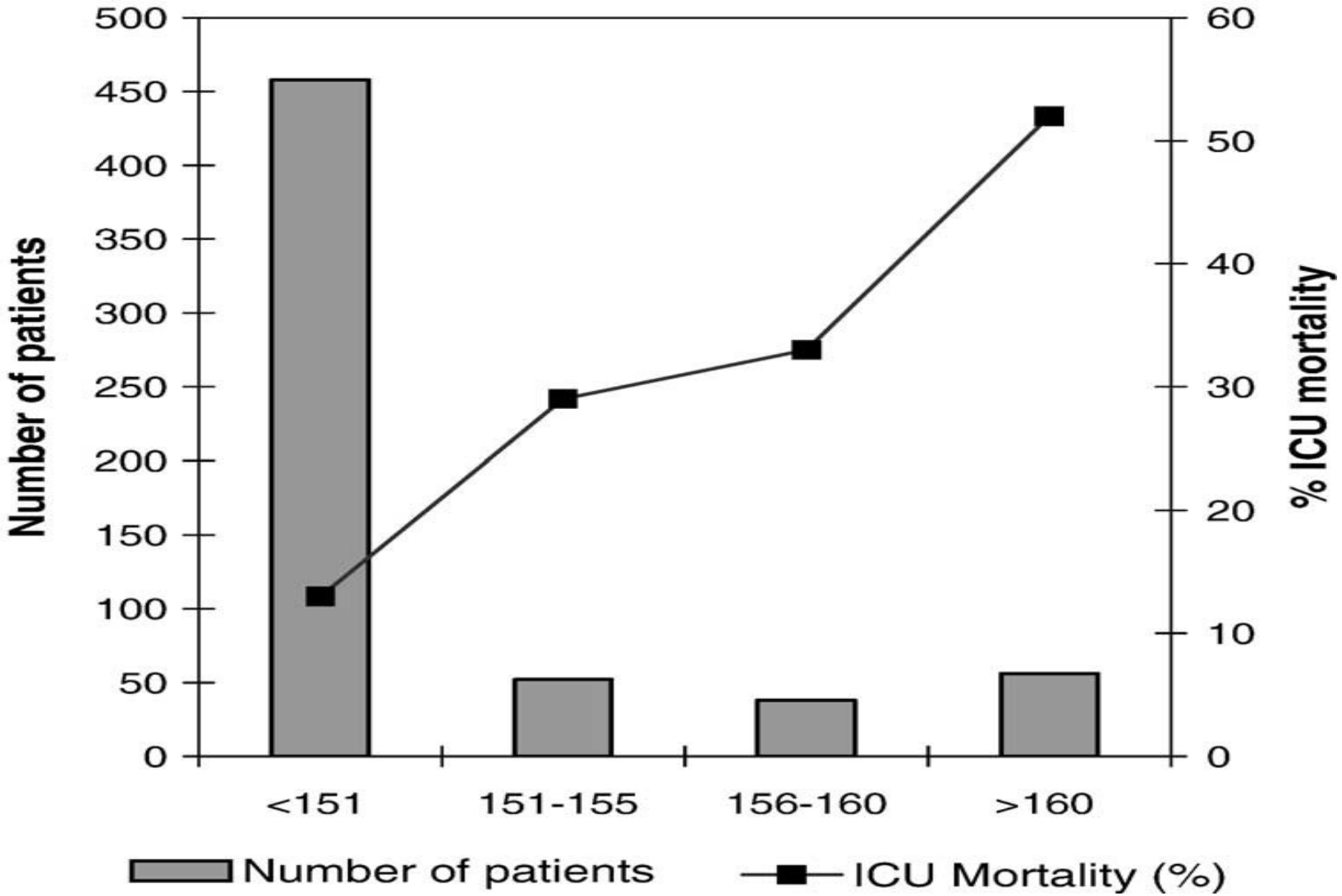


Hypernatremia Is Associated with Increased Risk of Mortality in Pediatric Severe Traumatic Brain Injury

Journal of Neurotrauma 2013

- Among 165 patients, 18% had hypernatremia (151–160 mmol/L), and 6% had severe hypernatremia (> 160 mmol/L)
- Mortality rate was four-fold and six-fold greater with hypernatremia and severe hypernatremia, respectively
- Survivors with hypernatremia had greater PCCU and hospital lengths of stays

Influence on the outcome - Do we know what we are doing ?



death, even after adjustment for baseline risk.

Influence on the outcome :
Do we know what we are doing ?

Author and year	Study type	Serum sodium cutoff defining hypernatremia	Population size (N)	ICU type	Incidence of ICU-acquired hypernatremia	Length of ICU stay (d)	Mortality
Lindner et al [13]	Retrospective	145 mmol/L	2.314	Surgical	10%	17 vs 3 ($P < .01$)	19% vs 8% ($P < .01$)
Stelfox et al [15]	Retrospective	145 mmol/L	6.727	Surgical	4%	4 vs 2 ($P = .69$)	14% vs 2% ($P < .001$)
Darmon et al [12]	Retrospective	145 mmol/L	8.441	Mixed	11% (mild) 4% (moderate to severe)	13 vs 5 ($P < .001$)	30% (mild), 46% (moderate to severe) vs 15% ($P < .001$)
O'Donoghue et al [16]	Retrospective	150 mmol/L	3.317	Mixed	8%	13 vs 2 ($P < .001$)	22% vs 3% ($P < .001$)
Stelfox et al [14]	Retrospective	145 mmol/L	8.142	Mixed	26%	7 vs 2 ($P < .001$)	23% vs 9% ($P < .001$)
Hoorn et al [45]	Retrospective	150 mmol/L	1.843	Mixed	7%	11 vs 3 ($P < .001$)	48% vs 10% ($P < .001$)
Lindner et al [10]	Retrospective	150 mmol/L	981	Medical	7%	20 vs 8 ($P < .001$)	43% vs 24% ($P < .01$)
Polderman et al [76]	Retrospective	150 mmol/L	389	Medical	6%	13 vs 5 ($P < .01$)	32 vs 20 ($P < .01$)

Influence on the outcome : Do we know what we are doing ?

Pay attention to minimal serum sodium change

Darmon M et al. Critical Care. 2013

- Observational study on a prospective database – 14 years (n=11125).

- After adjustment for confounder,

- Mild (>145) = sHR 1.34, 95% CI 1.14 to 1.57
- Moderate (>150) = sHR 1.51, 95% CI 1.15 to 1.99
- Severe (>155) = sHR 2.64, 95% CI 2.00 to 3.81

Outcome analysis and outcome predictors of traumatic head injury in childhood: Analysis of

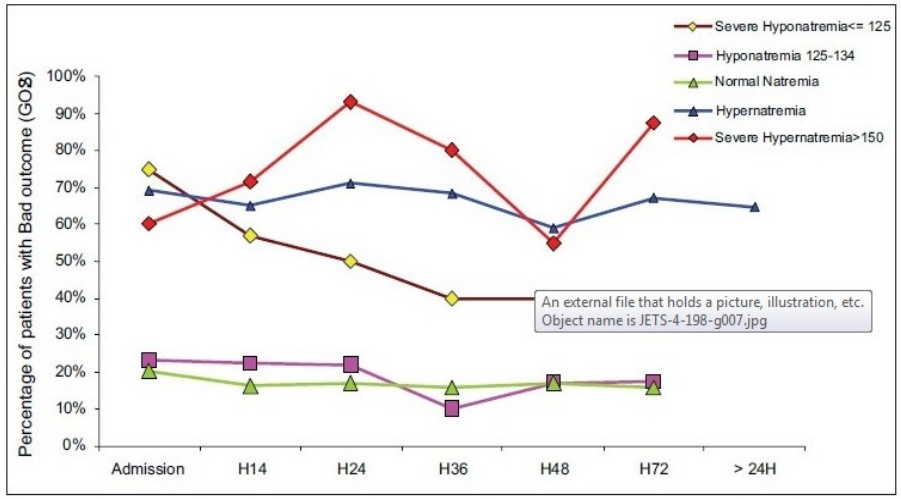
www.ncbi.nlm.nih.gov/pmc/articles/PMC3132359/?report=printable

Hypernatremia (>145 mmol/l)	30 (8.6)	46 (44.9)	<0.001

FIGURES IN PARENTHESIS ARE IN PERCENTAGE

Association between each secondary systemic insult and outcome

Figure 1



Association between dysnatremia [on admission; 12 hours after ICU admission (H12); ....] and bad outcome

J Emerg Trauma Shock

J Emerg Trauma Shock

Both severe hyponatremia and hypernatremia are associated with bad outcome!!

Our Data

Design: Retrospective analysis of prospective data.

Setting: Level III PICU of tertiary care teaching hospital.

Period: July – 2004 to June – 2013

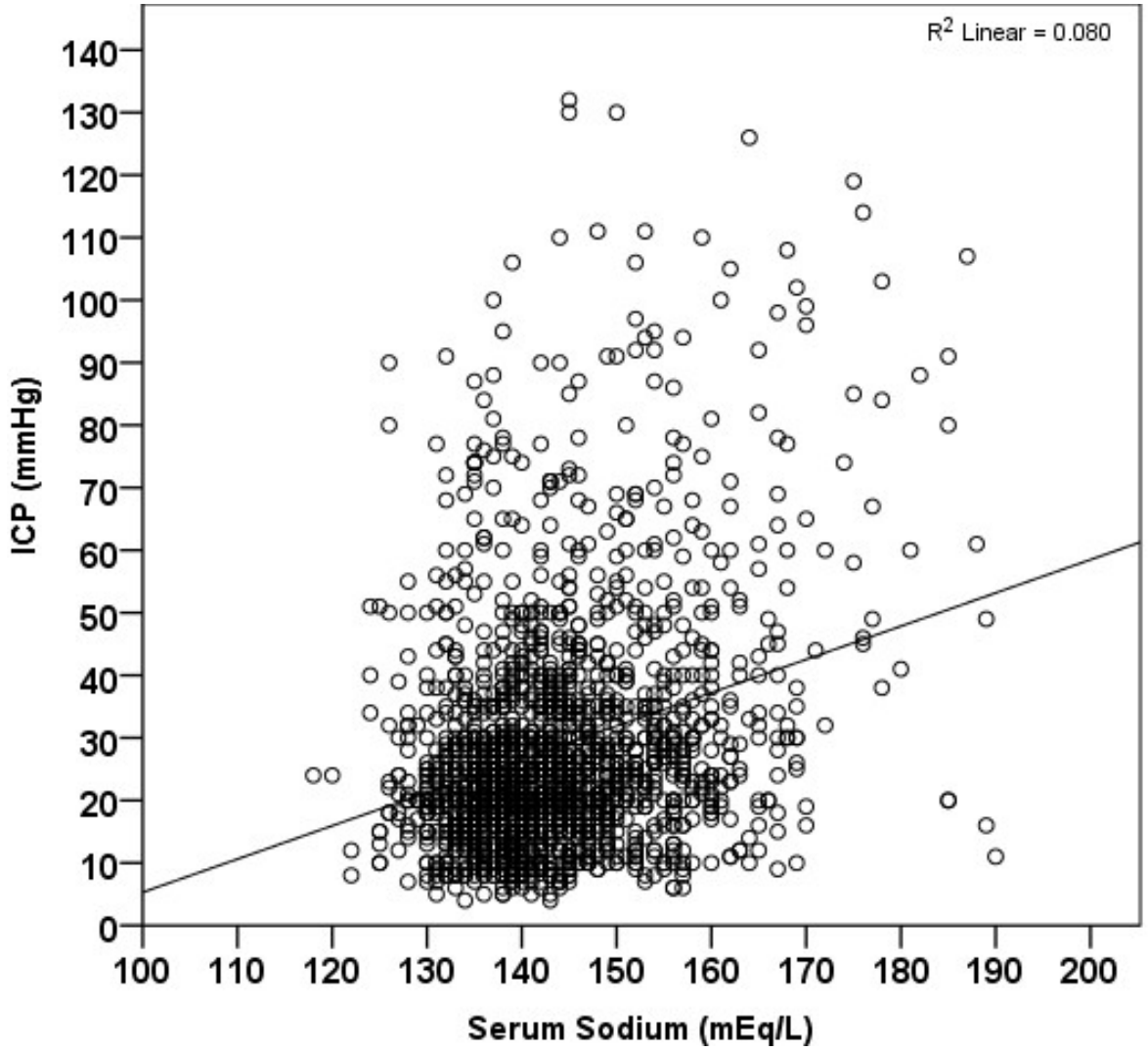
Participants

·251 children, aged 1 to 12 years, with

Method

- Each serum sodium value was matched with the highest corresponding ICP recorded before the next serum sodium was measured.
- 1799 pairs of serum sodium and ICP were analyzed.

Result

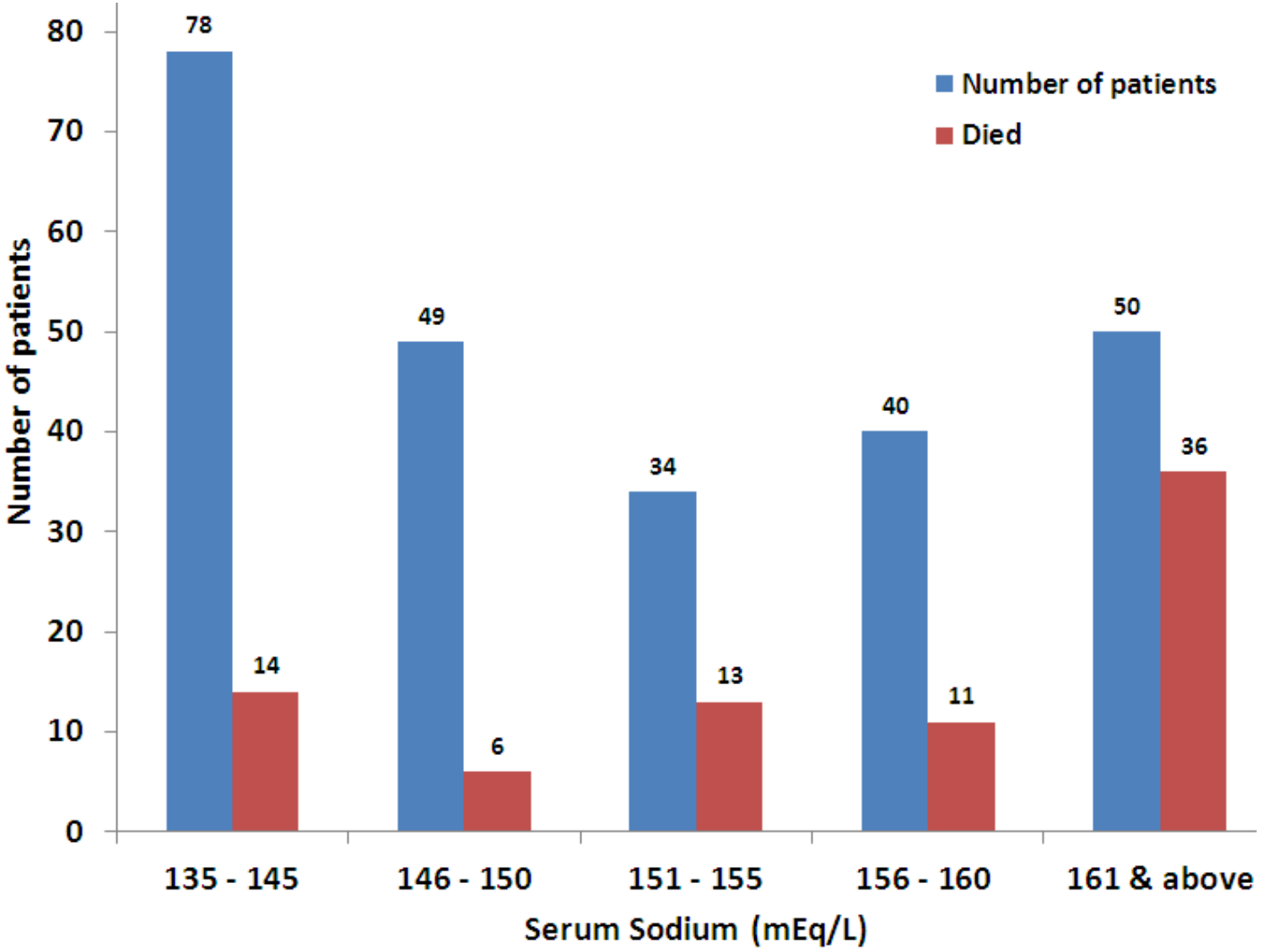


Person correlation

r= 0.284; p = <0.001

(Positive correlation)

Results : Outcome (n = 251)

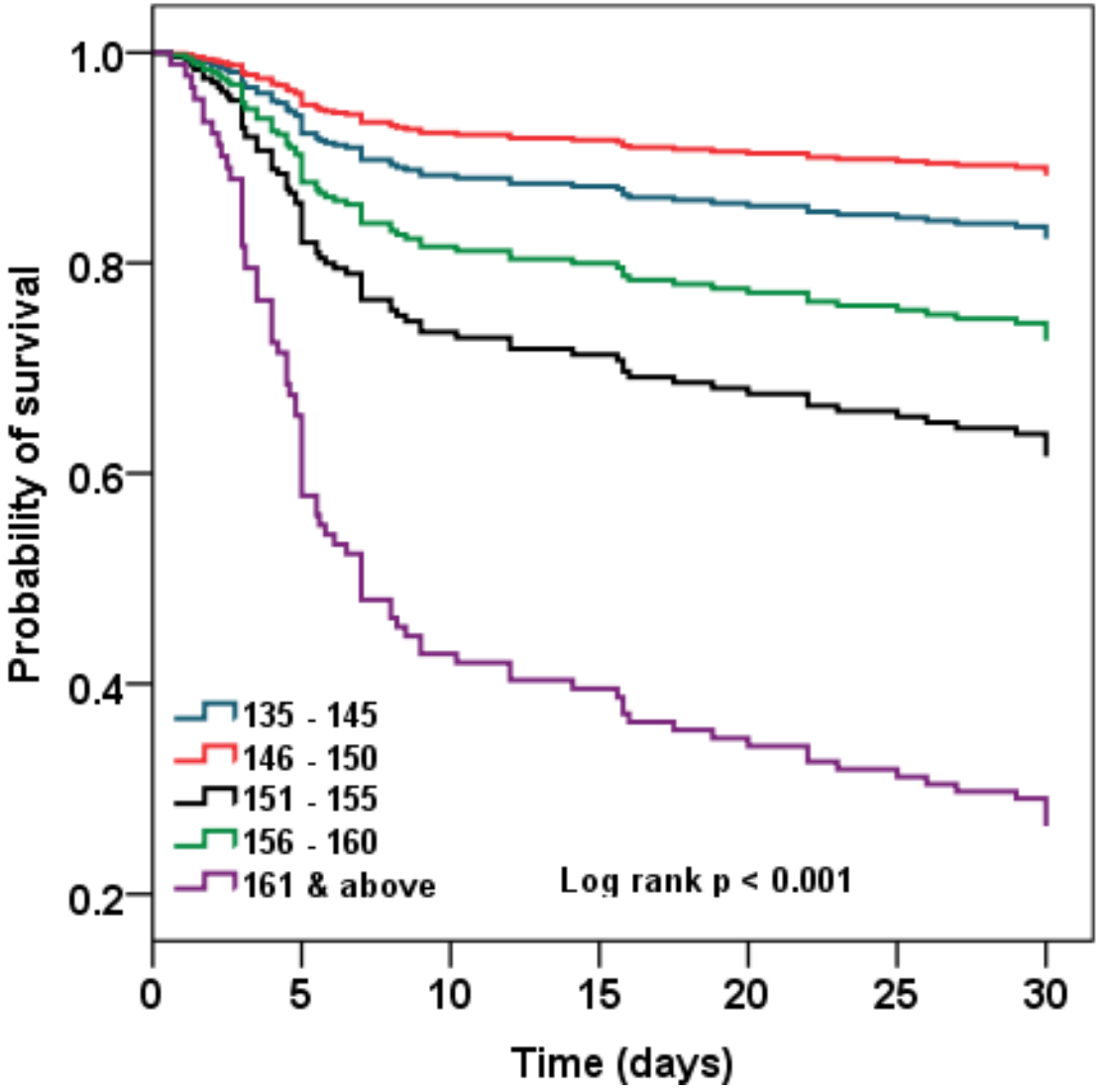


p = < 0.001

(Wilcoxon Signed Ranks Test)

(18%) **(12.2%)** **(38.2%)** **(27.5%)** **(72%)**

Probability of survival by 30-days



Independent predictor (n = 251)

Multivariate analysis

Variables	Beta Value	OR (95% CI)	p value
m-GCS score	0.336	1.4 (1.1 – 1.83)	0.013
Opening ICP	- 0.027	0.974 (0.952 – 0.995)	0.018
Serum Sodium 146 – 150	2.502	12.20 (4.6 – 32.36)	< 0.001
Serum Sodium 151 – 155	2.961	19.31 (6.1 – 61.47)	< 0.001
Serum Sodium 156 – 160	1.520	4.57 (1.6 – 13)	0.004
Serum Sodium 161 & above	2.043	7.71 (2.6 – 22.46)	< 0.001

Adjusted for Age, Sex, PRISM-III, Diagnosis, m-GCS score, opening ICP

Current stand: optimal sodium level

- Normal Sodium is ideal
- Using hypertonic saline therapy -145 – 150 meq/L ?

But… The optimal dose ??

- Across various etiologies

- Without resulting in nephrotoxicity, rebound