Contribution of fluids and electrolyte management to lung injury

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Doctor of Philosophy

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Summary

Fluid administration and electrolyte management is perhaps the most common intervention in hospital. Acute lung injury is common in critically ill patients and is associated with increased morbidity and mortality. The current literature suggests that administration of fluids is not straightforward and there are concerns of potential harm with fluid administration. Similarly electrolyte abnormalities are known to have adverse effects in critically ill patients. This work focuses on the effects of fluid and electrolyte management on lung injury.

Effects of sodium, fluid boluses and osmolality on lung injury were separately investigated. I utilised animal models, healthy human volunteers, clinical and epidemiological studies to investigate the effects of fluid and electrolyte management on lung injury

Sodium: Current levels of sodium administration are more than three times the NHMRC recommendations in both adult and paediatric patients, most of which is derived from inadvertent sources such as drug infusions, drug boluses and flushes. Such high levels of administration lead to positive sodium balance which

in turn causes an expansion of the extracellular fluid compartment and is associated with respiratory dysfunction as evidenced by decreased oxygen levels and prolong length of invasive mechanical ventilation.

Fluid boluses: Utilising both basic sciences and clinical studies I found that bolus administration of intravenous fluids had minimal physiological benefit in the circumstances investigated and tended to be harmful. In patients with severe sepsis there was a decrease in oxygen levels after their administration, in healthy subjects after administration of 0.9% saline there was evidence of interstitial oedema, and in animal studies bolus i.v. fluids resulted in permeability pulmonary oedema despite a “safe” (non-hydrostatic) left heart pressure. Such lung injury after administration of fluid boluses is possibly through activation of endothelial calcium ion channels (transient receptor potential vanilloid 4 (TRPV4) channels. This fluid induced lung injury was prevented by administration of a relatively specific TRPV4 blocker (ruthenium red).

Hyperosmolality: Using animal studies I found that induced hypernatremia was lung protective in acute lung injury, independent of fluid or sodium load. Based on my animal work, I hypothesised that lung-protective effects of hypernatremia would reduce its general adverse effects, leading to amelioration of the increase in mortality risk in patients with lung injury. To examine

this we utilised a large administrative database (from the Australia New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE)) and found that high admission serum sodium was associated with an increased odds for ICU death, except in respiratory patients.

In critically ill patients (i) inadvertent sodium administration is common which leads to a large positive sodium balance which is associated with adverse respiratory effects (ii) bolus administration of fluid can induce lung injury, and (iii) induced hyperosmolarity may be lung protective.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Shailesh Bihari

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ABBREVIATIONS AND SYMBOLS

ACCP American College of Chest Physicians

AIDS Acquired immunodeficiency syndrome

AKI Acute kidney injury

ALI Acute lung injury

ANG2 Angiopoietin 2

ANOVA Analysis of variance

ANP Atrial naturitic peptide

ANZICS–APD Australian and New Zealand Intensive Care Society Adult Patient Database

ANZPICR Australian and New Zealand Paediatric Intensive Care Registry;

APACHE Acute physiology and chronic health evaluation

ARDS Acute respiratory distress syndrome

ATS American thoracic society

BAL Broncho alveolar Lavage

BiPAP Bi-phasic positive airway pressure

BIVA Bioelectrical impedance vector analysis

BMI Body mass index

BP Blood pressure

Ca^{2+} Calcium

CCI Charlson co-morbidity index age adjusted score.

CHF Chronic heart failure

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CRRT Continuous renal replacement technique

CVP Central venous pressure

CVVH Continuous veno-venous haemofiltration

CVVHDF Continuous veno-venous haemodiafiltration

DLCO Diffusing capacity of the lung for carbon monoxide

dX/dV Delta reactance/delta lung volume

ECF Extracellular fluid

Echo Echocardiography

EDD Extended daily dialysis

EELV End expiratory lung volume

EET Epoxyeicosatrienoic acid

ERS European respiratory society

F female

FB Fluid boluses

FEV_1 Forced expiratory volume in one second

FFP Fresh frozen plasma

FILI Fluid induced lung injury

FiO2 Fraction of inspired oxygen

FRC Functional residual capacity

FVC Forced vital capacity

GCS Glasgow coma scale

GFR Glomerular filtration rate

HDU High dependency unit

HR Heart rate

HTS Hypertonic saline

i.v. Intravenous

IC Inspiratory capacity

ICF Intra-cellular fluid

ICU Intensive care unit

ID Subject identification number.

IFNγ Interferon gamma

IOS Impulse Oscillometry system

IQR Inter-quartile range

ITGV Intra thoracic gas volume

LIS Lung Injury score

LOS Length of stay

LPS Lipopolysaccharide

LVOT Left ventricular outflow tract

M Male

MAP Mean arterial pressure

MPO Myeloperoxidase

MV Mechanical ventilation.

NA Not applicable

NHMRC National Health and Medical Research Council

Na^+ Sodium

NIBP non-invasive blood pressure

OR Odd's ratio

OT Operation theatre

PaO_2 Partial pressure of arterial oxygen

PEEP Positive end expiratory pressure

PEFR Peak expiratory flow rate

PFT Pulmonary function test

PGI_2 Prostacyclin

PICU Paediatric intensive care unit

PIM Paediatric Index of Mortality;

PLA_2 Phospholipase A_2

PLR Passive leg raising

PRC Packed red blood cells;

RAAS Renin angiotensin aldosterone system

ROC Receiver operating characteristic.

RR Respiratory rate

RRT renal replacement technique

RV Residual volume

SAPS Simplified acute physiology score

SBL supine body length.

SCCM Society of Critical Care Medicine Consensus Conference

SD standard deviation.

SD Standard deviation

SEM Standard error of the mean

SOFA Sequential organ failure assessment score.

TBW Total body water

TLC Total lung capacity

TNF-α Tumour necrosis factor alpha

TPN Total parental nutrition

TRP Transient receptor potential

TRPV Transient receptor potential vanilloid

U Unit

USG Ultrasonography

VWF von Willebrand factor

V_T Tidal volume

VTI Velocity time integral

WPBs Weibel–Palade bodies

SYMBOLS

↑	Increased/elevated
↓	Decreased/reduced
<	Less than
≤	Less than or equal to
>	Greater than
≥	Greater than or equal to
#	Number
ρ	rho
°	Degrees
Ω	Ohm
~	Approximately/no substantial change

PREFACE

This preface is to certify that several chapters within this thesis contain content that is substantially unchanged from the content of multi-author papers which have either been published or are being prepared for publication, (**Appendix 5**) which may lead to some repetition of ideas. The following statements outline the contribution of all authors to the content of manuscripts that have been included in this thesis.

Chapter 1 Introduction

Book Chapter : Bihari S and Bersten AD. Sodium loading in critical care - textbook "Diet and Nutrition in Critical Care" under "Specific nutrients" published by Springer 2013

Bihari S: Proposed the design of the literature review, determined the search terms and completed the search strategy, data extraction, data synthesis and analysis and interpretation, before preparation the initial draft and revisions of the manuscript

Bersten AD: Contributed to the literature review design, interpretation of results and revisions of the manuscript

Chapter 3 Sodium administration in ICU patients

Bihari S, Ou J, Holt AW, Bersten AD. Inadvertent sodium loading in critically ill patients. Crit Care Resusc. 2012;14:37.

Bihari S: Proposed the study design, and completed data collection, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Ou J: Helped with data collection

Holt A: Modified the original idea and contributed to the manuscript revision

Bersten AD: contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Peake SL, Seppelt IM, Williams P, Bersten AD. Sodium administration in critically ill patients in Australia and New Zealand: a multi-centre point prevalence study Crit Care Resusc 2013; 15: 294-300.

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Peake SL: Contributed to the study design and revisions of the manuscript

Seppelt IM: Contributed to the conduct of the point prevalence study

Williams P: Contributed to the study design

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Taylor S, and Bersten AD. Inadvertent sodium loading with renal replacement therapy in critically ill patients. J Nephrol. 2014 Feb 4. [Epub ahead of print]

Bihari S: Proposed the study design, and completed data collection, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Taylor S: Contributed to the study design

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Festa M, Peake SL, Seppelt IM, Williams P, Wilkins B and Bersten AD. Sodium administration in critically ill paediatric patients in Australia and New Zealand: a multi-centre point prevalence study. Crit Care Resusc 2014; 16: 112-118.

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Festa M: Contributed to the study design and revision of the manuscript

Peake SL: Contributed to the study design and revisions of the manuscript

Seppelt IM: Contributed to the conduct of the point prevalence study

Williams P: Contributed to the study design

Wilkin B: Contributed to the data interpretation

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Chapter 4 Sodium balance in ICU patients

Bihari S, Baldwin C and Bersten AD. Fluid balance does not predict estimated sodium balance in critically ill mechanically ventilated patients. Crit Care Resusc 2013; 15: 89-96

Bihari S: Proposed the study design, and completed data collection, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Baldwin C: Contributed to the bioelectrical impedance spectroscopy measurement and revision of the manuscript

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Peake S, Prakash S, Saxena M, Campbell V, Bersten AD. Sodium balance, not fluid balance, is associated with respiratory dysfunction in mechanically ventilated patients: a prospective, multi-centre study. Manuscript accepted in Crit Care Resusc 2015

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript .

Peake SL: Contributed to conduct of study at her study centre – The Queen Elizabeth Hospital (South Australia) and revisions of the manuscript

Prakash S: Contributed to the data analysis

Saxena M: Contributed to conduct of study at his study centre – St. George Public Hospital, Sydney NSW

Campbell V: Contributed to conduct of study at his study centre – Nambour Hospital (QLD)

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Chapter 5 Fluid bolus

Bihari S, Prakash S, Bersten AD. Post resuscitation fluid boluses in patients with severe sepsis and septic shock (PRICE study). Shock 2013; 40: 28-34

Bihari S, Prakash S, Bersten AD. Early changes in serum electrolytes and acid-base status with administration of 4% albumin. Intensive Care Med. 2014; 40:1392-3.

Bihari S: Proposed the study design, and completed data collection, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Prakash S: Contributed to the data collection

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Wiersema U, Schembri D, Depasquale C, Dixon D, Lawrence M, Bowden J, Dixon D and Bersten AD. Interstitial pulmonary edema despite normal echocardiographic indices in healthy volunteers following 0.9% Saline bolus when compared with 4% albumin and 5% glucose. Manuscript under review

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript
Wiersema U: Contributed to conduct of study with echocardiographic measurements
Schembri D: Contributed to conduct of study with respiratory measurements
Depasquale C: Contributed to conduct of study with echocardiographic interpretations and revision of the manuscript
Dixon D: Contributed to the study with laboratory measurements and revision of the manuscript
Lawrence M: Contributed to the study with laboratory measurements
Bowden J: Contributed to conduct of study with respiratory interpretations and revision of the manuscript
Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Dixon D, Lawrence M and Bersten AD. Ruthenium red inhibits intravenous fluid induced permeability lung oedema suggesting a TRPV4 mechanism. Manuscript under review

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript
Dixon D: Contributed to the animal study design, data interpretation and manuscript preparation
Lawrence M: Contributed to the study with PCR and ELISA measurements (results not included in the PhD)
Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Chapter 6 Effect of serum sodium and osmolality on lung injury

Bihari S, Peake S, Bailey M, Pilcher D, Prakash S, Bersten AD. Admission high serum sodium is not associated with increased ICU mortality risk in respiratory patients. J Crit Care. 2014 [Epub ahead of print].

Bihari S: Proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Peake SL: Contributed to the study design and revisions of the manuscript

Bailey M: Contributed to the statistical analysis and revision of the manuscript

Pilcher D: Contributed to the study design

Prakash S: Contributed to the data analysis

Bersten AD: Contributed to the study design, interpretation of results and revisions of the manuscript

Bihari S, Dixon D, Lawrence M and Bersten AD. Induced hypernatremia reduces acute lung injury, independent of fluid or sodium load. Manuscript under review

Bihari S: proposed the study design, analysis and interpretation, before preparation of the initial draft and revisions of the manuscript

Dixon D: Contributed to the animal study design, data interpretation and manuscript preparation

Lawrence M: Contributed to the study with PCR and ELISA measurements (results not included in the PhD)

Bersten AD: contributed to the study design, interpretation of results and revisions of the manuscript.